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BIOMARKERS OF EXPOSURE TO TOXIC SUBSTANCES
Volume III: Proteomics
Biomarkers to Kidney and Organ Damage

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14. ABSTRACT

Early detection of kidney malfunction can help to prevent permanent kidney damage. During the normal physiological state, predominantly low molecular weight proteins pass freely through the glomerular barriers; whereas some middle range molecular weight (and almost no high molecular weight) proteins can get through the renal tubules. Consequently, negligible amounts of protein are excreted into the urine. However, strenuous activity can cause dehydration, decreased blood flow, as well as the build-up of toxic chemicals—thereby multiplying the risk of kidney damage. Knowledge of urinary protein biomarkers would be ideal for the early detection of kidney malfunction/disease, since urine is readily available and easy to collect. As such, we utilized proteomic and metabonomic techniques (Liquid chromatography coupled to mass spectrometry, two dimensional difference in-gel electrophoresis) to monitor/quantitate changes in urinary protein abundance or post-translational modifications in the well established D-serine and puromycin nephrotoxin models. D-serine selectively damages renal proximal tubes in rodents, while puromycin causes transient visceral epithelial cell injury accompanied by heavy proteinuria. We observed numerous changes in levels of different proteins that can be very useful for early diagnostics of kidney malfunctions caused by different toxicants.

15. SUBJECT TERMS

Amphotericin B, bioinformatics, cell cycle regulation, clinical, clustering analysis, D-serine, glomerular injury, hippuric acid, histopathologic analysis, microarray, pathway analysis, proximal tubular damage, puromycin, renal injury, transcription regulation

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TABLE OF CONTENTS

Section **Page**

LIST OF FIGURES

Figure **Page**

LIST OF TABLES

Table **Page**

FORWARD

This research program is documented in a final technical report comprised of five volumes. Volume I provides a global overview of the entire effort. Volumes II-IV provide the technical details of the three approaches (genomics, proteomics, and metabonomics) used to identify the relevant biomarkers of toxic effects. Volume V describes the effort to perform pre-validation of the identified biomarkers. Figure 1 shows this technical report structure.

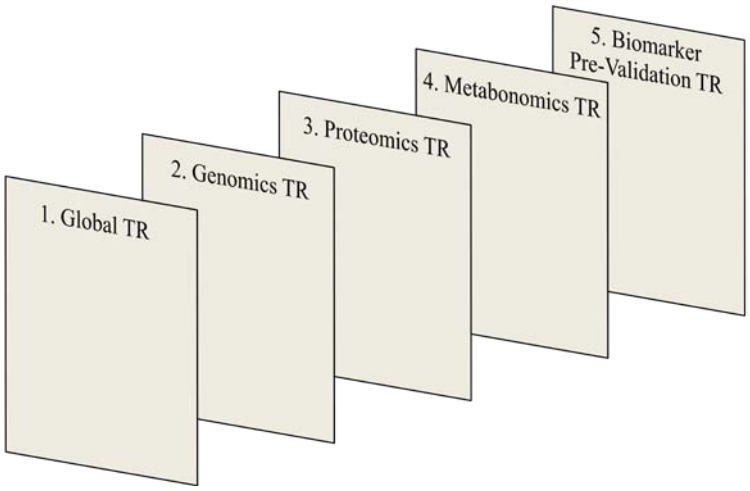

Figure 1: Technical Report Volume Order

Volume I contains the experimental design, explains how the needs of the warfighter led to conducting this research effort, the reasoning behind the specific analysis method and biomarker selections, and the manner in which the specimens were collected. The sample analysis is captured in Volumes II-IV (Genomics, Proteomics, and Metabonomics). The three analytical and investigational approaches were conducted in parallel and fed data into Volume V (Biomarker Pre-validation) as depicted in Figure 2.

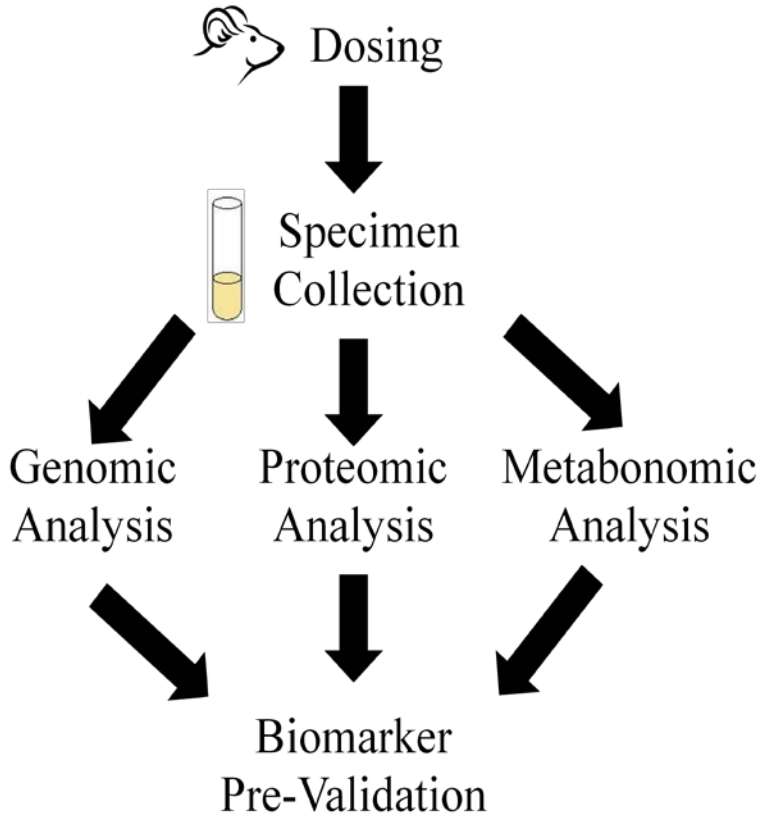

Figure 2: Work Unit Investigational Overview

Over 80 Department of Defense civilians, contractors, and military contributed in the research spanning five years.

SUMMARY

Early detection of kidney malfunction can help to prevent permanent kidney damage. During the normal physiological state, predominantly low molecular weight proteins pass freely through the glomerular barriers; whereas some middle range molecular weight (and almost no high molecular weight) proteins can get through the renal tubules. Consequently, negligible amounts of protein are excreted into the urine. However, strenuous activity can cause dehydration, decreased blood flow, as well as the build-up of toxic chemicals—thereby multiplying the risk of kidney damage. Knowledge of urinary protein biomarkers would be ideal for the early detection of kidney malfunction/disease, since urine is readily available and easy to collect. As such, we utilized proteomic and metabonomic techniques (Liquid chromatography coupled to mass spectrometry, two dimensional difference in-gel electrophoresis) to monitor/quantitate changes in urinary protein abundance or post-translational modifications in the well established D-serine and puromycin nephrotoxin models. D-serine selectively damages renal proximal tubes in rodents, while puromycin causes transient visceral epithelial cell injury accompanied by heavy proteinuria. We observed numerous changes in levels of different proteins that can be very useful for early diagnostics of kidney malfunctions caused by different toxicants.

1. INTRODUCTION

Environmental exposure to toxicants as well as therapeutic interventions often causes nephrotoxicity. An expanded list of proteins and metabolites that indicate kidney damage would help immensely to monitor renal conditions after exposure to external toxicants, in pharmaceutical drug safety evaluations and in clinical studies.

It has been shown that high doses of D-serine are nephrotoxic in rats (Ganote et al., 1974). D-serine causes selective necrosis after reabsorption in the proximal straight tubules of rat kidney. In contrast, L-serine does not show any nephrotoxic effect (Ganote et al., 1974). The advantage of using the D-serine model is to reveal early and sensitive biomarkers for epithelial cell injury in kidneys. The mechanism of D-serine-induced toxicity is not yet completely understood. However, it has been proposed that tyrosine catabolism and D-amino acid oxidase activity might be involved in D-serine toxicity (Ferguson et al., 2008).

Metabonomics is a rapidly emerging technique while proteomics is well established tool in biomarker discovery research. Metabonomic profiling is a very powerful approach that enables identification of changes in small molecule levels in biological fluids. Differentiated metabolites can serve as biomarkers for the health status of an organism. The renal damage by D-serine in rats is initiated by injury to tubular epithelial cells in various nephron segments or by injury to specific cell types in the glomerulus (Ganote et al., 1974). If damage repair is not accomplished in time, accumulation of extracellular matrix can lead to irreversible fibrosis.

2. METHODS

2.1 Proteomics

2.1.1 Proteomics via two dimensional difference in-gel electrophoresis (2D DIGE) approach

2.1.1.1 Urine Sample Protein Separation Using 2D DIGE.

Urine was collected at 24 hour intervals from male Fischer 344 rats (Charles River Laboratories, Wilmington, MA) weighing 222-258 gram (g) at the beginning of the study. Rats were housed in metabolic cages for urine collection. Three time points were utilized in this study (0, 24 and 48 hr). Treated animals received a single intraperitoneal dose of D-Serine at 500 mg/kg. Control animals received vehicle only (0.9% saline). All animal procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals, National Research Council, 1996, and the Animal Welfare Act of 1966, as amended. Urine was collected with 1ml of 1% sodium azide at the bottoms of the collection tubes to control bacterial growth. Collected samples were frozen at -20°C until analysis.

Samples were prepared for DIGE analysis by removal of contaminants and concentration of proteins using GE Healthcare's 2-D Clean-Up Kit following the manufacturer's instructions. The purpose of this step is to remove salts and other non-protein species. The pellets of the cleaned samples were redissolved in the labeling buffer (7 M urea, 2 M thiourea, 4% 3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS), 30 mM Tris pH 8.8) and Bradford Assays were performed to determine protein concentration in each sample. It was critical to determine the accurate amount of protein in the samples in order to ensure reliability of the latter quantitation analysis. For the assay, the standard and sample solutions were typically prepared in triplicate with the concentrations in the range of 1-10 ug/ml and placed in 96 well plates. The UV absorbance of the solutions was measured via plate reader with diode array detection. To decrease the variations due to differences of the wells and detection channels, the readings were averaged as measured by two different positions: one is normal position; the other is after 180^{o} rotation. The concentrations of the samples were determined by the averages of 6 measurements. Only results with relative standard deviations of less than 5% were accepted. Once the concentrations of the samples were determined, the samples were diluted to 1mg/ml with labeling buffer. Equal volumes were removed from each sample and pooled. A portion of the pooled samples were labeled with fluorescence dye CyDye2 to serve as the internal standard, and the rest were utilized later for the preparative gel. A 50 ul aliquot of each sample (1mg/ml) was labeled with either fluorescence dye CyDye 3 or CyDye 5. The labeling ratio was 1 ug protein to 8 pmol of dye. Samples were randomly labeled with CyDye 3 or CyDye 5. Following the labeling, two samples labeled with CyDye 3 and CyDye 5 (randomly combined) were mixed with the CyDye 2 labeled internal standard and 320 uL rehydration buffer (7 M urea, 2M thiourea, 2% CHAPS, 100 mM dithiothreitol and 0.5% immobilized pH gradient (IPG) buffer). After centrifugation, 450 ul of the supernatant was removed and used to rehydrate 24 cm pH 4-7 isoelectric focusing (IEF) strips overnight. Isoelectric focusing was performed on the rehydrated strips in four steps: 1) 500 V for 1 hr; 2) 500-1000 V for 1 hr 4 min; 3) 1000-10000 V for 3 hr; and 4) 10000 V for 3 hr 28 min. Total focusing time was 8 hr 32 min, resulting in 52500 V per

strip. The strips were placed in a bagged sample tray and stored at -80^{o}C until use. Prior to use, focused IPG strips were equilibrated for 15 min in equilibration buffer with 1% DTT to reduce disulfide bonds, followed by 15 min in equilibration buffer containing 2.5% iodoacetamide to alkylate the thiols and excess of DTT. Strips were then rinsed with SDS running buffer (25 mM Tris, 192 mM Glycine, 0.1% sodium dodecyl sulfate (SDS) w/v) and applied onto 12.5 % acrylamide/bis-acrylamide gels (1 mm, 20 x 25 cm, lab-cast). The second dimension was run on a DaltTwelve system with 1X running buffer in the lower chamber and 2X running buffer in the upper chamber. The second dimension was run under the following conditions: 2W per gel for 45 min and 15 W per gel for about 4 hrs. When multiple gels run at one time, lower wattage and longer running time were usually needed to decrease the generation of heat. Following the second dimension, the gels were scanned on a Typhoon imaging system (GE HealthCare). Differential In-gel Analysis (DIA) was performed for each gel with Decyder Software, version 6.5 (GE HealthCare). Then, Biological Variation Analysis (BVA) was performed. The Internal Standard (IS) image with the greatest number of spots was chosen as the master gel and landmarks were set to help the inter-gel matching. Two-way Anova analysis was performed for both time and dose, and spots with p values < 0.05 for dose, time and interaction were analyzed further. The preparative gel was prepared slightly different: bind silane was put on the short plate to fix the gel onto the glass plate to prevent the gel from deforming. A higher concentration of sample (500 ug) was loaded and separated via IEF and SDS PAGE. After separation, the gel was stained with Lava Purple and scanned on a Typhoon imaging system. After matching the preparative gel with the master gel, a pick list was generated for protein spots with significant differential expression.

2.1.1.2 Protein Sample Analysis Utilizing LTQ LC-MS/MS

Gel plugs containing the selected spots were reduced in 10mM DTT for 30 min before being alkylated with 50mM Iodoacetamide in the dark for 30 min. Proteins were in-gel digested overnight with trypsin at 37°C. The digestion was stopped by adding of an acidic solution and the peptides were extracted from the gel plugs via 60 min incubation in 50 µl of 50% Acetonitrile, 0.1% Trifluoroacetic acid (TFA). Eluted peptides from the in-gel digest were concentrated to approximately 5ul using a Speed Vac concentrator. Samples were desalted with a C18 zip-tip (Millipore) and the eluted peptide mixture was concentrated to 5µl. The concentrate was then acidified and diluted to 12µl with 0.1% Formic Acid prior to LC-MS analysis. The desalted samples were loaded onto 96 well plates in the autosampler of a nano ultrahigh performance liquid chromatography (UPLC; Waters) which allowed for continuous acquisition of data. For each sample analyzed, 3µl of the mixture was loaded onto a 75 µm x 20cm BEH 130 C18 capillary column and separated on-line. Separation of the peptides was performed with a 60 min gradient of 2% to 50% B (A, 0.1% Formic acid; B, 99.9% Acetonitrile, 0.1% Formic acid) at 0.250 µl/min. The eluted peptides were ionized by electrospray using a commercially available nano-spray source (New Objective). Nano-spray allows for much greater sensitivity than standard electrospray. Ionization of the peptides was done at a voltage of 2.0 kV. For each analysis, approximately 7500 scans were acquired.

2.1.1.3 Data Analysis and Protein Identifications

Protein identification was accomplished by use of data dependent MS2 spectra acquired on a Thermo Fisher LTQ-XL instrument (San Jose, CA). The XCalibur data acquisition software

(Thermo Fisher) was set up to acquire a full scan of the entire mass range. The three most abundant peaks were selected for higher mass resolution analysis and MS2 analysis on the LTQ instrument for structural information. Fragmentation by Collision Induced Dissociation using Helium gas was used. Dynamic exclusion was set in order to gain information on low abundant peptides. Following data collection, the MS2 spectra were searched against a Uniprot/TrEMBL database using both the MASCOT (Matrix Science) and Sequest algorithms. A protein was considered as a match if 2 or more peptides were identified using set parameters within the searching algorithms. A peptide was only considered if it met the criteria for a significant match.

2.1.2 Proteomics via label free technique

2.1.2.1 Rat Urine Gel Filtration and Digestion

Rat urine samples were centrifuged at 13,000 rpm for 10 minutes to remove particulates. The supernatants were collected for further processing. Low molecular weight components and salts in rat urine were removed using Pharmacia NAP-10 column. The protein concentrations were determined with a Bio-Rad BCA protein assay using bovine serum albumin as a reference. 1% RapiGest SF (Waters, Milford, MA) stock solutions were mixed with rat urines to yield the final concentration 0.1% for digestion enhancement. The mixtures were equilibrated at 37°C for 2 minutes. Proteins were reduced (50mM dithiothreitol in 50 mM ammonium bicarbonate) at 60°C for 30 minutes, alkylated (100 mM Iodoacetamide) at room temperature for 30 minutes in the darkness, then digested overnight at 37°C with trypsin (1:50, w/w). The digestion was terminated with 45 minutes incubation in formic acid at 37°C. Acid treated samples were centrifuged at 13,000 rpm for 10 minutes. Supernatants were further concentrated using SpeedVac (Eppendorf).

Trypsin digested samples were analyzed in triplicate using a Waters nanoAcquity UPLC system (Milford, MA) on-line with a Thermo Finnigan LTQ XL (San Jose, CA) equipped with a TriVersa nanomate electrospray ionization (ESI) source from Advion BioSystems (Rockville, MD). The LC-MS/MS work flow consisted of a 75 μm x 20cm BEH 130 C18 capillary column to separate peptide mixtures, nano electrospray ionization source (which converts eluted peptides into gas phase ions), ion trap mass analyzer (which separates ions based on the mass to charge difference), and a detection (to detect the relative abundance of ions at different m/z values). In MS/MS mode, precursor ions were recorded in full scan mode for all m/z values. Data-dependent MS/MS method was used to acquire the data, followed by selective ion isolation and fragmentation. The MS/MS spectra were further searched against the GenBank nonredundant database using the SEQUEST search engine which is included in Sieve software package (ThermoFisher). Peptides and proteins identifications, chromatographic alignment and statistical analysis were performed. MS intensities from the raw LC/MS data were used to find the statistical differences between peptides and proteins at the different time points after the D-serine uptake. For each time point, three replicates were analyzed.

2.1.2.2 Data Analysis

We compared the rat urine profiling for three different conditions: control, 24 hour and 48 hour. SIEVE™ (version beta 5) differential expression software (ThermoFisher) was utilized

for the further automated label-free quantitative data analysis. SIEVE employed the algorithm ChromAlign™ for the first chromatographic alignment step in time and m/z. The parameters were set as Correlation Bin Width 2, Tile Increment 150, Tile Maximum 300, Tile Size 300 and Tile Threshold 0.6. Recursive quantitative base peak framing (called BioSIEVE™) was processed next in order to find differences that were statistically meaningful for the biomarker discovery, which generated 80270 frames with the mass to charge from 300 to 1800 and retention time from 10 to 90 minute. Additional SEQUEST searches were completed for the peptide and protein identification. Protein assignment and quantitation were based on the identified peptides. Among the identified proteins in the LC-MS/MS experiment, some proteins were differentially expressed under the three conditions with at least 2 peptides identified, the desired maximum $p<0.05$, minimum cross correlation score (XCorr) of 1.8 for +1, 2.5 for +2, and 3.5 for +3 charged ions. By comparing spectral information from LC/MS analyses of control, 24 hour and 48 hour rat urine samples after D-serine intake, protein changes among the three sample sets were used to assess differential protein expression.

2.1.3 Immunohistochemistry

Kidneys were placed in Davidson's solution (glacial acetic acid, 95% ethyl alcohol, 10% neutral buffered formalin and water in a 1:3:2:3 ratio) containing a trace of eosin to provide differential color. After 24 hours, tissue was placed sequentially into 70%, 90%, 100% ethyl alcohol, 24 hours for each incubation. Kidneys were mounted in paraffin blocks and section slices 10um thick were obtained using Ergostar HM 200 Rotary Microtome (ThermoFisher Scientific) followed by placement on microscope slides.

Previously fixed and mounted kidney slices were placed onto heating blocks at 55°C for ten minutes to melt the paraffin. Paraffin was removed from slides via 2 washes of xylenes for 10 minutes. Slides were rinsed twice for 2 minutes in 100% alcohols (18:1:1, 100% ethanol: 100% methanol:100% isopropanol) followed by two, 2 minute rinses in a 95% solution of the 100% alcohols. Slides were then placed in an 80% solution of the 100% alcohols for 2 minutes followed by 5-6 washes with deionized water for 2 minutes each. Slides were incubated in blocking solution that consisted of 3% IgG free bovine serum albumin (Jackson Immunoresearch Laboratories, West Grove, PA, USA) in Tris Buffered Saline Buffer (TBS; 100 mM Tris pH 7.4, 138 mM NaCl, 27 mM KCl) containing 0.1% Nonidet P40 (TBSN) overnight at 4°C. Antibody incubations were performed in TBSN supplemented with 3% IgG free bovine serum albumin. Primary antibodies were diluted 1:100, while secondary antibodies were diluted 1:200. Samples were incubated for 2 hours with the primary antibodies and 1 hour with the secondary antibodies. Both incubations were conducted at RT on orbital shaker at low speed. Slides were washed 5 times for 5 min each in TBSN. The in-house generated rabbit polyclonal GSC 1239 and GSC 1242 antibodies were used to stain against Group Specific Component (GSC) protein, while the in-house generated rabbit polyclonal hornerin-like protein (HLP) 1240 and HLP 1241 antibodies were used to stain Hornerin protein. All primary antibodies were designed and generated by Dr. Camilla Mauzy's group. Donkey anti-rabbit, FITC-labeled antibody (Jackson Immunoresearch Laboratories, West Grove, PA, USA) were used as secondary antibody. After the final wash, slides were quickly rinsed twice in TBS and dried at room temperature. A drop of ProLong Gold antifade reagent with 4′,6-Diamidino-2-phenyindole (DAPI; Invitrogen, Carlsbad, CA, USA) was applied onto the slides. Slides were covered with cover slips and images were taken using

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BD Pathway 435 confocal bioimager (BD BioSciences, Rockville, MD, USA). All images were taken under the same conditions.

2.2 Metabonomics

2.2.1 LC/MS Based Metabonomic Sample Analysis

Urine was centrifuged at 12,000 g for 5 minutes to remove particulates and filtered using a Pall Acrodisc 13 mm syringe filter with a 0.2 um GHP membrane prior to analysis. Samples were stored at 4°C until they were run. Analysis was completed using a Waters UPLC with an Acquity UPLC BEH C18 column (2.1 X 100 mm) held at 40°C. Water with 0.1% formic acid was used as mobile phase A and acetonitrile with 0.1% formic acid was used as mobile phase B. The gradient increased from 2%B to 98%B over 11 minutes followed by re-equilibration at 98%A with a flow-rate of 0.25 ml/min.

The UPLC was coupled to a Micromass Q-ToF micro mass spectrometer (Waters, Milford, MA). The electrospray conditions were capillary voltage, 3200; sample cone voltage, 35.0 and extraction cone voltage, 1.5. The desolvation temperature was 320°C and the source temperature was 130°C. Nitrogen was used as the cone gas.

Survey scan data was acquired in centroid mode from 80-1000 m/z with a scan time of 0.4s and an inter-scan delay of 0.1s. For accurate mass measurements, a reference compound, leucine enkephalin ($[M+H]^+$: 556.2771) (Sigma-Aldrich, St. Louis, MO) was run periodically using a lockspray source. The lockspray signal was set to acquire every 720s and two scans were averaged for each run. Urine samples were run in duplicate and analyzed using in-house software to determine peaks of interest.

For collection of fragmentation data (MS/MS), random urine samples were run using data dependent acquisition. The instrument was set to automatically switch on up to three ions in each survey scan whose intensity exceeded 150 counts/second. Survey data was acquired with a scan time of 1.0s and an inter-scan delay of 0.1s. MS/MS data was acquired for each precursor ion for up to 10s or until signal decreased below 30 counts/second with a scan time of 0.5 second (s) and an inter-scan delay of 0.1 s. Up to five different collision energies were scanned-20, 25, 30, 35, and 40 electronVolts (eV) using argon as the collision gas. Centroid data was collected from 50-750 m/z.

Standards were purchased from Sigma-Aldrich (St. Louis, MO) and run at 1 mg/ml (1ug injection) under the same conditions as the samples.

2.2.2 Metabonomic Data Analysis

In house developed software package was used to analyze the data. Only peaks with $p \leq 0.05$ were considered. The software package allows filtering data in any order, by masses, intensities, p values, counts, doses, time points, fold changes. The graphical presentation is also part of the package and allows detailed visualization of the analyzed data.

The software was written in MatLab environment. It was developed as collaborative effort by scientists from 711 Human Performance Wing (HPW)/Biotechnology Branch, Biosciences and Protection Division (RHPB) and Wright State University.

3. RESULTS AND DISCUSSION WITH CONCLUSIONS

3.1 Proteomics

3.1.1 D-serine toxicity assessment

3.1.1.1 D-serine toxicity assessment using 2D DIGE technique

Table 1 shows rats that were used for urine collection for D-serine toxicity study. Total number of samples was 30. Urine was collected from 10 rats using metabolic cages. Urine was collected into 50 ml tubes positioned on ice. The collection tubes contained 1ml of 1% sodium azide to prevent bacterial growth. Measured protein concentrations before and after clean-up procedure are shown in Table 2. The protein concentrations in different samples are quite comparable before and after clean-up procedure. Protein concentrations for animal number 251 are not shown. The animal has died during the study due to an infection. That is why we excluded partial set of urine samples (0 hr and 24 hr) for animal 251 from our study.

Table 1: Animals used in study

		Sampling Points		
Treatment	Rat	0 hr (A)	24 hr (B)	48 hr (C)
Control	242	242 A	242 B	242 C
	243	243 A	243 B	243 C
	244	244 A	244 B	244 C
	245	245 A	245 B	245 C
	246	246 A	246 B	246 C
Dosed	247	247 A	247 B	247 C
	248	248 A	248 B	248 C
	249	249 A	249 B	249 C
	250	250 A	250 B	250 C
	251	251 A	251 B	251 C

Table shows assigned numbers to the animals used in the D-Serine toxicity study. Animals 242 through 246 are control animals that received 0/9% saline solution injection. Dosed animals 247-251 received 500 mg/kg D-Serine injection. A, B,and C correspond to 0 hr, 24 hr and 48 hr sampling points, respectively.

Table 2: Protein concentrations before and after clean up procedure

Sample ID:	Before Precipitation (ug/ul)	After Precipitation (ug/ul)
242A	3.02	12.80
242B	3.26	9.24
242C	3.06	9.78
243A	3.01	9.67
243B	2.49	9.26
243C	3.40	9.42
244A	2.85	9.67
244B	2.25	8.80
244C	2.47	11.22
245A	2.70	8.28
245B	2.14	7.28
245C	2.57	10.42
246A	3.36	8.08
246B	2.52	9.52
246C	2.96	10.45
247A	2.16	10.63
247B	4.01	12.00
247C	1.92	11.43
248A	0.78	8.46
248B	2.83	10.27
248C	1.92	10.37
249A	2.42	8.26
249B	4.49	14.32
249C	2.87	11.66
250A	2.68	9.86
250B	3.50	13.31
250C	3.25	12.85

Protein from rat urine samples was precipitated using 2D clean up kit from GE Healthcare. Protein concentrations are shown before and after clean up procedure. Protein concentrations from animals 242 through 250 are shown. A, B and C are 0 hr, 24 hr and 48 hr sampling points, respectively.

150 ug of total protein was separated on IEF strips (pH3-10). The strips were subsequently loaded onto 2D gels. Total fifteen 2D gels were run. Table 3 shows what samples were loaded on each gel after labeling with Cy Dyes and IEF separation.

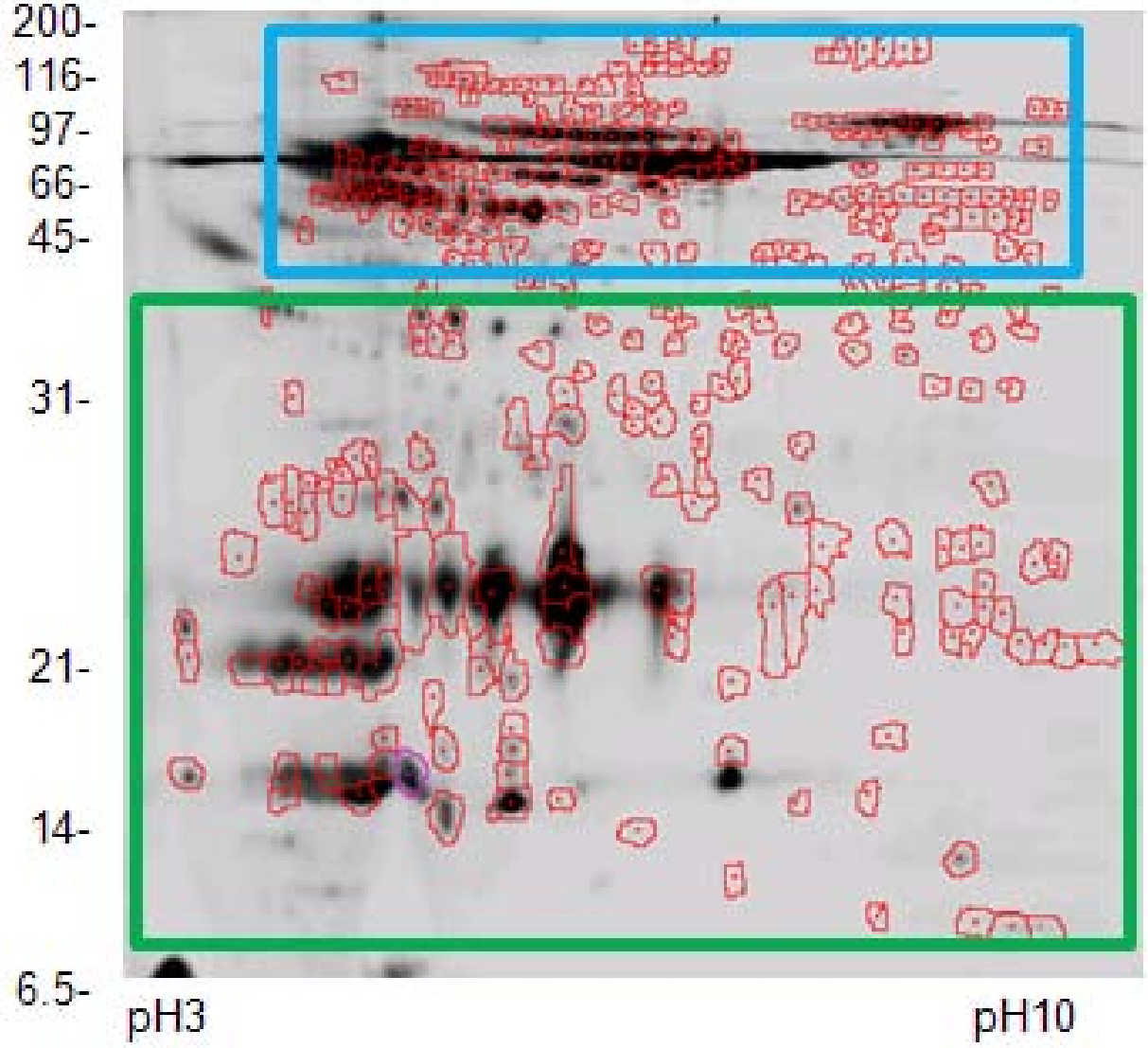
Table 3: Sample composition for each gel

Gel #	Cy2	Cy3	Cy5
Gel01	50 μg IS	50 μg 242A	50 μg 247A
Gel02	50 μg IS	50 μg 242B	50 μg 248B
Gel03	50 μg IS	50 μg 242C	50 μg 249C
Gel04	50 μg IS	50 μg 248A	50 μg 243A
Gel05	50 μg IS	50 μg 249B	50 μg 243B
Gel06	50 μg IS	50 μg 250C	50 μg 243C
Gel07	50 μg IS	50 μg 244A	50 μg 249A
Gel08	50 μg IS	50 μg 244B	50 μg 250B
Gel09	50 μg IS	50 μg 244C	50 μg 251C
Gel10	50 μg IS	50 μg 250A	50 μg 245A
Gel11	50 μg IS	50 μg 251B	50 μg 245B
Gel12	50 μg IS	50 μg 247C	50 μg 245C
Gel13	50 μg IS	50 μg 246A	50 μg 251A
Gel14	50 μg IS	50 μg 246B	50 μg 247B
Gel15	50 μg IS	50 μg 246C	50 μg 248C

Sample composition for each gel is shown in the Table. 150 ug of total protein after IEF separation was loaded on each gel. Internal standards, controls and samples from dosed animals were labeled with Cy 2, 3 and 5, respectively.

A total of 45 2D gel images (3 samples per gel, for each dye) were analyzed with DeCyder software. Images of the preparative gel are shown in Figure 3. A total of 3,141 spots were detected by the Decyder Analysis software (these include dust particles, artifacts etc.). 350 of these spots passed the two-way analysis of variance (ANOVA) cut-off of $P \leq 0.05$, showing they can differentiate conditions. 184 spots with the best p values were cored out and subjected to the protein identification procedure. Table 4 represents a list of unique proteins that were identified in the study. Generally, Mascot score over 50 is considered as a true identification of a protein. We considered proteins with two or more identified peptides only as it reflects true identification of a protein. The fold changes reflect negative and positive changes.

A



B

C

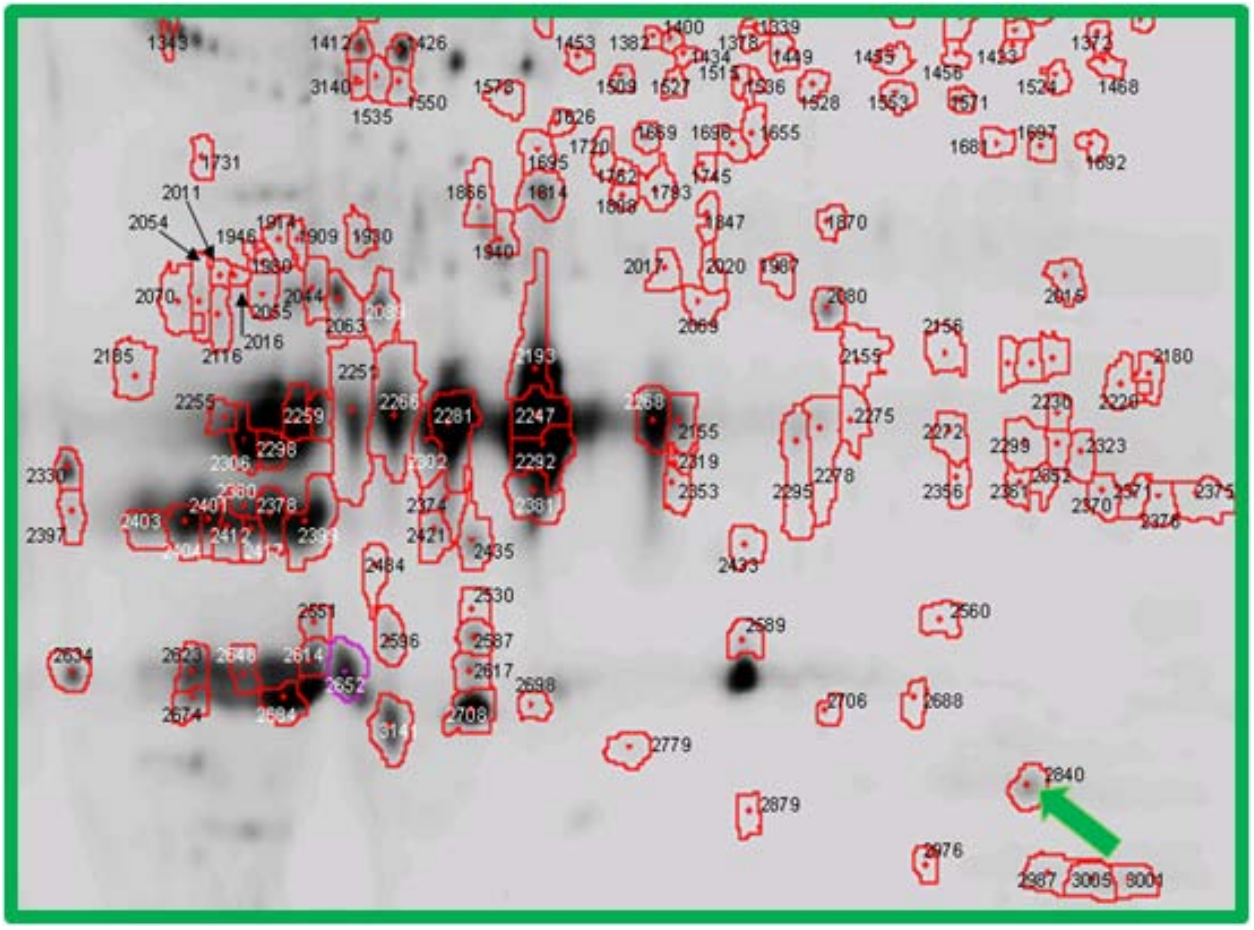


Figure 3: Preparative gel images

Preparative gel image is shown on panel A. Panels B and C show zoomed areas outlined in blue and green on Panel A, respectively. Spot numbers can be seen on Panels B and C.

Table 4: List of potential biomarkers identified in urine of rats after 500 mg/kg D-serine exposure

Accession	Protein Name	Unique peptides	Mascot Score	Average Ratio
A2AS84_MOUSE	Dipeptidylpeptidase 4	3	101	2.15
P70565_RAT	Plakoglobin	11	192	2.96
Q642C9_RAT	Meprin 1 alpha	9	198	2.78
Q80XP1_MOUSE	Complement Component 3	8	174	5.65
Q6DK74_XENTR	UGDH protein	2	72	3.95
Q99N59_RAT	alpha-amylase	>15	415	-1.64
Q5DT20_HUMAN	Hornerin	16	361	7.42
Q6MG79_RAT	Complement component 4	3	173	2.38
Q4LE79_HUMAN	DSP variant protein	2	68	2.64
Q5T0I2_HUMAN	Gelsolin	2	112	2.1
Q5M7V3_RAT	LOC367586 protein (Igg)	9	167	2.18
Q540A3_SCHJA	Clone ZZD245 mRNA sequence	2	62	3.2
Q6IAZ4_HUMAN	Aldo-keto reductase family 1	7	82	3.66
Q5XI43_RAT	Limitrin	2	69	3.99
Q3U5N9_MOUSE	Bone marrow macrophage cDNA	5	122	-1.65
Q3TF08_MOUSE	Retinol Binding Protein 4 fragment	3	113	3.44
Q5M9K1_MOUSE	Transthyretin	2	90	-1.76
Q499V5_RAT	Psbpc2 protein	3	112	-2.03
Q0PNI0_BUBBU	Alpha-lactalbumin	3	74	-2.57
Q17QL7_BOVIN	LOC507464 protein	3	113	-2.61
Q91Z73_MOUSE	Beta-2-microglobulin	2	83	2.01

Table shows proteins that were identified in single spots only. Accession numbers, corresponding protein names of the proteins and number of unique peptides identified are shown. Mascot scores and fold changes are shown. Negative and positive ratios reflect decrease and increase in the amount of protein (dosed vs. control), respectively.

Protein identification from the gel plugs revealed that many proteins were identified in multiple spots. That indicates that proteins in urine undergo extensive posttranslational modifications (PTMs) prior to, as well as after, being excreted by kidney. A handful of the identified proteins are peptidases that can contribute to the observed PTMs. In order to simplify the list of potential biomarkers caused by D-serine in rat urine, proteins identified in multiple spots are represented in Table 5.

Table 5: List of proteins identified in multiple spots as potential biomarkers in urine of rats after 500 mg/kg D-serine exposure

Accession	Protein	Number of Spots	Trend
Q7TMC7_RAT	Ab2-417, transferrin precursor	17	up
Q80ZA3_RAT	Alpha-2a ntiplasmin (serine)	3	up
Q8K1Q6_RAT	alpha2u globu lin	21	down
Q5I0M3_RAT	Complement component factor h-like 1	2	up
Q6IRS6_RAT	Fetub protein	3	up
Q9JL97_RAT	GPI-anchored ceruloplasmin	9	up
Q68FY4_RAT	Group specific component	8	up
Q0VAC5_HUMAN	Haptoglobin	2	up
Q3UKP2_MOUSE	Hemope xin	10	up
Q5D862_HUMAN	Ifaps oriasin	3	down
Q5M839_RAT	igh-1a pr otein	3	up
Q7TMB9_RAT	Liver regeneration pr otein lrryan	15	up
Q5M7V3_RAT	LOC367586 protein (Igg)	2	up
Q4KM66_RAT	LOC500183 protein	2	down
Q17QL7_BOVIN	LOC507464 protein	2	up/down
Q25468_9ASCI	Muscle actin	2	up
Q63581_RAT	Rat T-kininogen	8	up
Q546G4_MOUSE	serum a lbumin pr ecursor	16	up

Table shows proteins that were identified in multiple spots. Accession numbers and corresponding protein names of the identified proteins are shown. Up and down trends (dosed vs. control) are shown. Only trends over 2 fold were considered.

Graph Views of two selected proteins are shown in Figure 4. Group Specific Component (Gc), also known as vitamin D-binding protein, is responsible for the clearance of actins from the blood in response to injury and cell necrosis (Meier et al., 2006). Gc was identified in 8 spots showing increase in the range from 3.5 to 7.5 fold in our study. Transthyretin (TTR), showed almost 2-fold decrease in response to D-serine exposure. The protein is normally found in serum and cerebrospinal fluid where it serves as a carrier of the thyroid hormone (T4) (Brouwer et al., 1986). TTR also acts as a carrier of vitamin A via association with retinol binding protein (Brouwer et al., 1986). It is also known to be associated with most amyloidal diseases leading to neurodegeneration and organ failure via amyloidal fibrils depositions (Saraiva et al., 1983). Besides all other functions TTR serves as a blood biomarker of malnutrition (Staus, 2002). This protein was reported in several toxicological studies previously (Meistermann et al., 2006).

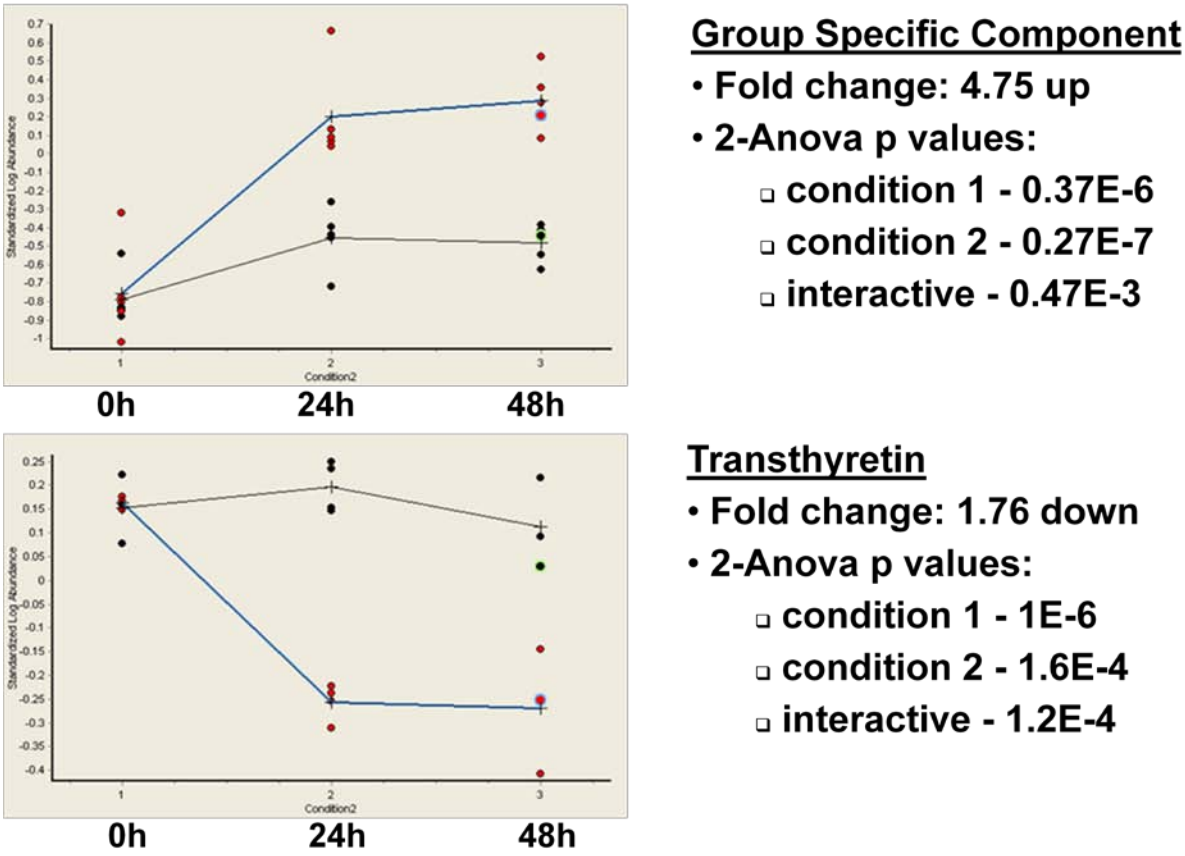


Figure 4: Group Specific Component (Gc) and Transthyretin (TTR) changes in response to D-serine treatment

Black and red dots correspond to 0 mg/kg and 500 mg/kg, respectively.

Notably, Gc, also known as vitamin D-binding protein, is responsible for the clearance of actins from the blood in response to injury and cell necrosis. According to the Gene Expression Data from Genomics Institute of the Novartis Research Foundation, Gc is expressed at 5 to 6-fold higher levels in rat's kidney than in any other tested organ or tissue. The gene expression data is shown in Figure 5.

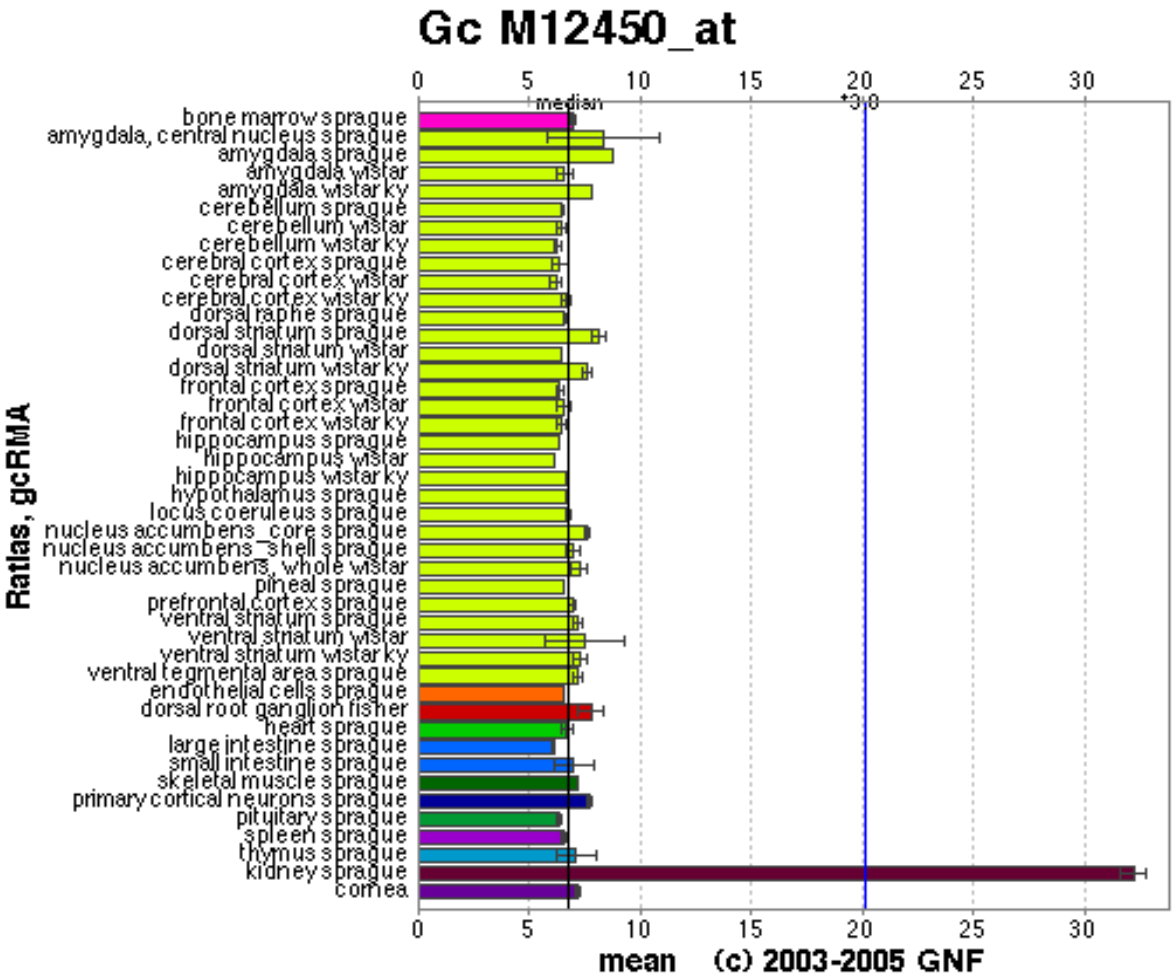


Figure 5: Gene expression of Gc in different organs and tissues of *Rattus norvegicus.*
The data is from Symatlas (Genomics Institute of the Novartis Research Foundation).

Immunostainings of kidney slices with antibodies against GSC confirmed that the protein level is elevated after the exposure to D-serine (Figure 6). The antibodies were raised by Dr. Mauzy's group. They were tested in Western blot analysis. Rat urine samples were probed with two different antibodies: GSC 1239 and GSC 1242. Antibody GSC 1239 exhibited much higher background when it was used for the Western blot analysis. Immunostainings confirmed the results of the Western blots. Only antibody GSC 1242 did not produce high nonspecific background. The level of Vitamin D binding protein is elevated when both sagittal and transverse sections of rat kidneys were probed with the GSC 1242 antibody.

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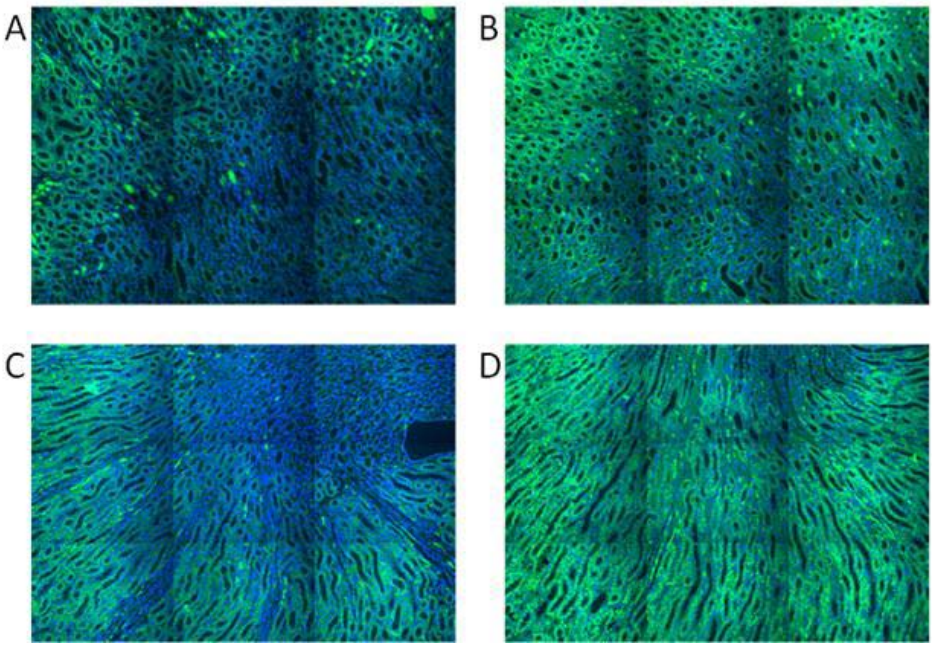

Figure 6: Immunostaining of kidney slices

Antibody GSC 1242 was used for staining. A and B – sagittal sections of kidney. C and D – transverse sections of kidney. A and C are controls at 12 hr. B and D are kidneys from animals after 500 mg/kg D-serine uptake, 12 rh.

Changes of two other proteins are shown in Figure 7 and Figure 8. β2-Microglobulin (B2M) is a known early biomarker of tubular dysfunction in a variety of conditions (Ferguson et al., 2008). It is typically filtered by the glomerulus and nearly completely reabsorbed and catabolized by the proximal tubular cells. The position of the B2M protein on the gel can be seen on Figure 3C. The green arrow points at spot 2840 where the protein was identified. B2M was elevated about 2-fold in our study. Hornerin appeared to be elevated almost 7.5-fold versus control (Figure 7). Position of the protein on the gel can be seen on Figure 3B. The green arrow points at spot 970 where hornerin protein was identified. The coverage of the protein is shown in Figure 8. Sequences of 15 unique peptides were identified by mass spectrometry in the study.

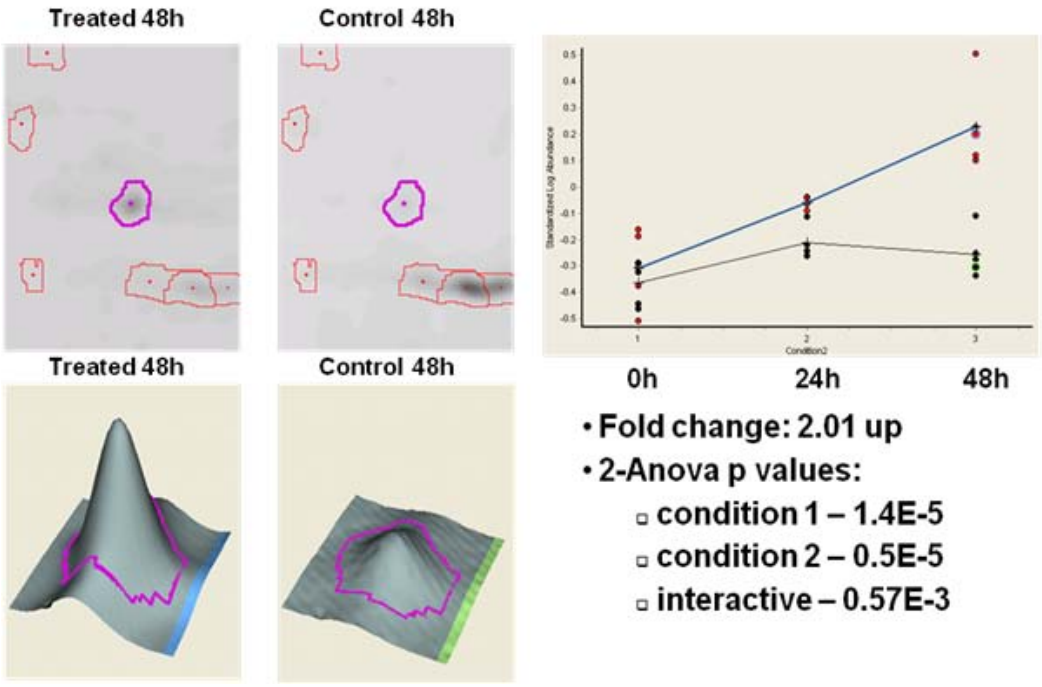

Figure 7: Graph and gel views of β2-Microglobulin changes in response to D-serine treatment

Black and red dots correspond to 0 mg/kg and 500 mg/kg, respectively.

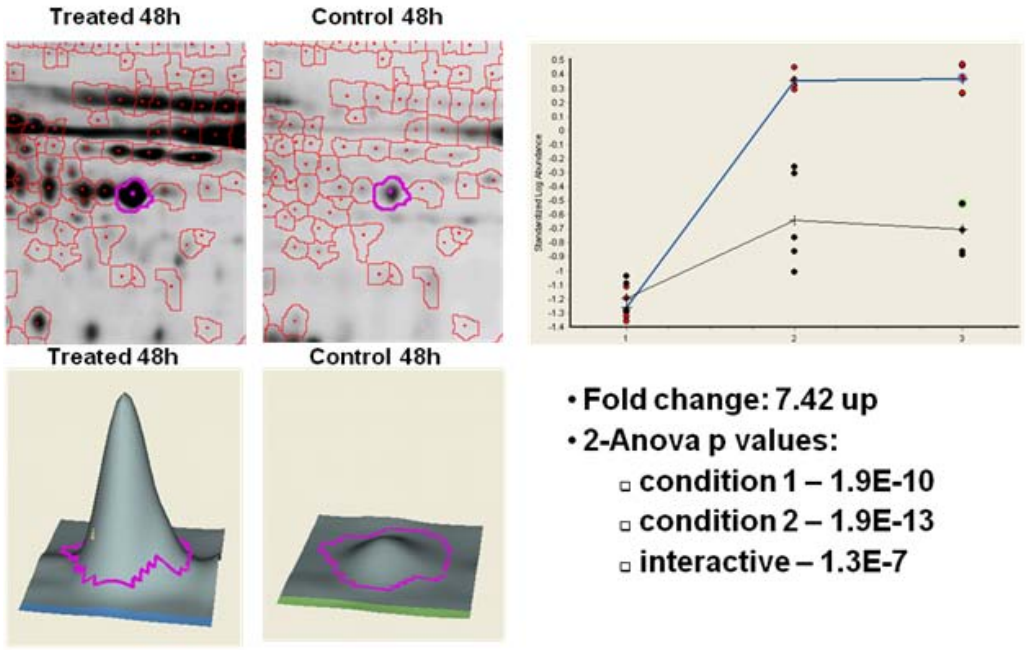

Figure 8: Graph and gel views of hornerin changes in response to D-serine treatment

Black and red dots correspond to 0 mg/kg and 500 mg/kg, respectively.

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>Q5U1F4|Q5U1F4_HUMAN Hornerin - Homo sapiens (Human).
MPKLLQGVITVIDVFYQYATQHGEYDTLNKAELKELLENEFHQILKNPNDPDTVDIILQS
LDRDHNKKVDFTEYLLMIFKLVQARNKIIGKDYCQVSGSKLRDDTHQHQEEQEETEKEEN
KRQESSFSHSSWSAGENDSYSRNVRGSLKPGTESISRRLSFQRDFSGQHNSYSGQSSSYG
EQNSDSHQSSGRGQCGSGSGQSPNYGQHGSGSGQSSSNDTHGSGSGQSSGFSQHKSSSGQ
SSGYSQHGSGSGHSSGYGQHGSRSGQSSRGERHRSSSGSSSSYGQHGSGSRQSLGHGRQG
SGSRQSPSHVRHGSGSGHSSSHGQHGSGSSYSYSRGHYESGSGQTSGFGQHESGSGQSSG
YSKHGSGSGHSSSQGQHGSTSGQASSSGQHGSSSRQSSSYGQHESASRHSSGRGQHSSGS
GQSPGHGQRGSGSGQSPSSGQHGTGFGRSSSGPYVSGSGYSSGFGHHESSSEHSSGYTQ
HGSGSGHSSGHGQHGSRSGQSSRGERQGSSAGSSSSYGQHGSGSRQSLGHSRHGSGSGQS
PSPSRGRHESGSRQSSSYGPHGYGSGRSSSRGPYESGSGHSSGLGHQESRSGQSSGYGQH
GSSSGHSSTHGQHGSTSGQSSSCGQHGATSGQSSSHGQHGSGSSQSSRYGQQGSGSGQSP
SRGRHGSDFGHSSSYGQHGSGSGWSSSNGPHGSVSGQSSGFGHKSGSGQSSGYSQHGSGS
SHSSGYRKHGSRSGQSSRSEQHGSSSGLSSSYGQHGSGSHQSSGHGRQGSGSGHSPSRVR
HGSSSGHSSSHGQHGSGTSCSSSCGHYESGSGQASGFGQHESGSGQGYSQHGSASGHFSS
QGRHGSTSGQSSSSGQHDSSSGQSSSYGQHESASHHASGRGRHGSGSGQSPGHGQRGSGS
GQSPSYGRHGSGSGRSSSSGRHGSGSGQSSGFGHKSSSGQSSGYTQHGSGSGHSSSYEQH
GSRSGQSSRSEQHGSSSGSSSSYGQHGSGSRQSLGHGQHGSGSGQSPSPSRGRHGSGSGQ
SSSYGPYRSGSGWSSSRGPYESGSGHSSGLGHRESRSGQSSGYGQHGSSSGHSSTHGQHG
STSGQSSSCGQHGASSGQSSSHGQHGSGSSQSSGYGRQGSGSGQSPGHGQRGSGSRQSPS
YGRHGSGSGRSSSSGQHGSGLGESSGFGHHESSSGQSSSYSQHGSGSGHSSGYGQHGSRS
GQSSRGERHGSSSGSSSHYGQHGSGSRQSSGHGRQGSGSGHSPSRGRHGSGLGHSSSHGQ
HGSGSGRSSSRGPYESRSGHSSVFGQHESGSGHSSAYSQHGSGSGHFCSQGQHGSTSGQS
STFDQEGSSTGQSSSYGHRGSGSSQSSGYGRHGAGSGQSPSRGRHGSGSGHSSSYGQHGS
GSGWSSSSGRHGSGSGQSSGFGHHESSSWQSSGCTQHGSGSGHSSSYEQHGSRSGQSSRG
ERHGSSSGSSSSYGQHGSGSRQSLGHGQHGSGSGQSPSPSRGRHGSGSGQSSSYSPYGSG
SGWSSSRGPYESGSSHSSGLGHRESRSGQSSGYGQHGSSSGHSSTHGQHGSTSGQSSSCG
QHGASSGQSSSHGQHGSGSSQSSGYGRQGSGSGQSPGHGQRGSGSRQSPSYGRHGSGSGR
SSSSGQHGSGLGESSGFGHHESSSGQSSSYSQHGSGSGHSSGYGQHGSRSGQSSRGERHG
SSSRSSSRYGQHGSGSRQSSGHGRQGSGSGQSPSRGRHGSGLGHSSSHGQHGSGSGRSSS
RGPYESRSGHSSVFGQHESGSGHSSAYSQHGSGSGHFCSQGQHGSTSGQSSTFDQEGSST
GQSSSHGQHGSGSSQSSSYGQQGSGSGQSPSRGRHGSGSGHSSSYGQHGSGSGWSSSSGR
HGSGSGQSSGFGHHESSSWQSSGYTQHGSGSGHSSSYEQHGSRSGQSSRGEQHGSSSGSS
SSYGQHGSGSRQSLGHGQHGSGSGQSPSPSRGRHGSGSGQSSSYGPYGSGSGWSSSRGPY
ESGSGHSSGLGHRESRSGQSSGYGQHGSSSGHSSTHGQHGSASGQSSSCGQHGASSGQSS
SHGQHGSGSSQSSGYGRQGSGSGQSPGHGQRGSGSRQSPSYGRHGSGSGRSSSSGQHGPG
LGESSGFGHHESSSGQSSSYSQHGSGSGHSSGYGQHGSRSGQSSRGERHGSSSGSSSRYG
QHGSGSRQSSGHGRQGSGSGHSPSRGRHGSGSGHSSSHGQHGSGSGRSSSRGPYESRSGH
SSVFGQHESGSGHSSAYSQHGSGSGHFCSQGQHGSTSGQSSTFDQEGSSTGQSSSHGQHG
SGSSQSSSYGQQGSGSGQSPSRGRHGSGSGHSSSYGQHGSGSGWSSSSGRHGSGSGQSSG
FGHHESSSWQSSGYTQHGSGSGHSSSYEQHGSRSGQSSRGEQHGSSSGSSSSYGQHGSGS
RQSLGHGQHGSGSGQSPSPSRGRHGSGSGQSSSYSPYGSGSGWSSSRGPYESGSGHSSGL
GHRESRSGQSSGYGQHGSSSGHSSTHGQHGSTSGQSSSCGQHGASSGQSSSHGQHGSGSS
QSSGYGRQGSGSGQSPGHSQRGSGSRQSPSYGRHGSGSGRSSSSGQHGSGLGESSGFGHH
ESSSGQSSSYSQHGSGSGHSSGYGQHGSRSGQSSRGERHGSSSGSSSHYGQHGSGSRQSS
GHGRQGSGSGQSPSRGRHGSGLGHSSSHGQHGSGSGRSSSRGPYESRSGHSSVFGQHESG
SGHSSAYSQHGSGSGHFCSQGQHGSTSGQSSTFDQEGSSTGQSSSYGHRGSGSSQSSGYG
RHGAGSGQSLSHGRHGSGSGQSSSYGQHGSGSGQSSGYSQHGSGSGQDGYSYCKGGSNHD
GGSSGSYFLSFPSSTSPYEYVQEQRCYFYQ

Figure 9: Human hornerin coverage

Peptides in red color were identified by mass spectrometry.

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Confirmed sequences of hornerin from mouse and human (UniProt Database) are 2,496 and 2,850 amino acids in length, respectively. Alignment performed on the two proteins mentioned above shows quite weak homology between hornerins of mouse and human origins (data not shown). We have noticed there are several portions of the hornerin protein sequence identified in our study that are covered by sequencing (Figure 8). Based on this fact one could suggest there is a high possibility of an alternative splicing of the hornerin, at least in rats. Two predicted rat hornerin-like protein sequences that can be found in the GeneBank Database do not show any significant homology to human or mouse hornerins (data not shown). The two predicted rat hornerin-like proteins do not share significant homology between themselves as well (data not shown). It appears a rat hornerin protein most likely exists, and it must be highly homologous to human hornerin but the sequence of this protein is not in current databases.

Hornerin protein is structurally most similar to profilaggrin. Profilaggrin protein belongs to a family of proteins that also includes trichohyalin, and repetin (Lee et al., 1993; Huber et al., 2005). All these proteins are involved in cornification process of the epidermis in many vertebrates, including humans. The members of this family exhibit EF-hand domains at their N-termini followed by multiple tandem repeats. The Ca^{2+} binding EF-hand domain shows significant homology with EF-hand domains of S100 proteins. Differentiation of primary mouse epidermal keratinocytes induced by Ca^{2+} ions results in the elevated hornerin expression (Makino et al., 2001). It was also reported that the tandem repeat unit A of hornerin protein exhibits strong antimicrobial features (Wu et al., 2007). The authors suggested that each molecule of hornerin protein might be converted into numerous active antimicrobial peptides. They also proposed the conversion is achieved through posttranslational cleavage.

Immunostainings of kidney slices with antibodies against hornerin confirmed that the protein level is significantly elevated after the exposure to D-serine (Figure 10). The antibodies were raised by Dr. Mauzy's group. They were tested in Western blot analysis. Rat urine samples were probed with two different antibodies: HLP 1240 and HLP 1241. Antibody HLP 1240 exhibited much higher background when it was used for the Western blot analysis. Immunostainings confirmed the results of the Western blots. Only antibody HLP 1241 did not produce high nonspecific background. The level of hornerin protein is significantly elevated when both sagittal and transverse sections of rat kidneys were probed with the HLP 1241 antibody.

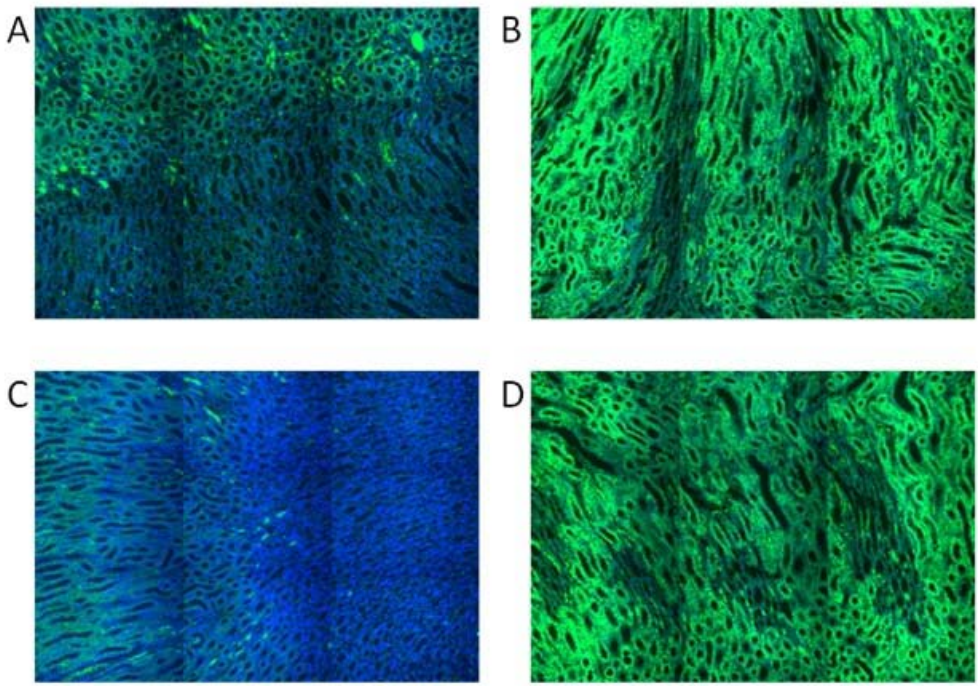


Figure 10: Immunostaining of kidney slices

Antibody HLP 1241 was used for staining. A and B – sagittal sections of kidney. C and D – transverse sections of kidney. A and C are controls at 12 hr. B and D are kidneys from animals after 500 mg/kg D-serine uptake, 12 hr.

Another protein, Liver Regeneration Factor, lrryan, showed up to 15-fold increase in our D-serine toxicity study. The protein exhibits extensive serpin homology. Serpins are involved in blood coagulation, compliment activation, fibrinolysis, angiogenesis, inflammation, tumor suppression, hormone transport (Zorio et al., 2008; Machado et al., 2006; O'Reilly, 2007; Ragg, 2007).

In the blood, serpins are about 2% of the total protein of which 70% is alpha-antitrypsin. Serpins are metastable proteins which interact with their substrate and irreversibly trap the acyl intermediate as a result of a major conformational change. Occurring imbalances between peptidases and their inhibitors can lead to a disease (Askew et al., 2008).

3.1.1.2 D-serine toxicity assessment using label free technique

Label free approach is different from 2D DIGE. The two techniques can complement each other. While protein dynamic range can be an issue for label free approach, 2D DIGE is less subjected to be skewed by that. It is especially true since samples for 2D DIGE are immunodepleted prior to use. However, even some of the medium abundance proteins can be masked on the gel by highly abundant protein spots. In case of label free technique, only very low abundant proteins are often not detected.

As for label free technique, 5ug protein from each urine sample is simply subjected to reduction, alkylation and trypsinization procedures as described in 2.1.2.1. The samples then run on reverse phase column interfacing LTQ FT mass spectrometer (Section 2.1.2.1). Label free

data analysis is accomplished using Sieve Software package. Thermo Scientific SIEVE software is an automated software package for the label free, semi-quantitative differential expression analysis of proteins, peptides and metabolites. It is a statistically rigorous tool for analyzing data from proteomic and metabolomic biomarker discovery experiments.

The same urine samples were used in this study as for 2D DIGE proteomic analysis. The samples are shown in Table 1. The results of data analysis performed by the SIEVE™ software package are shown in Appendix A. All p values are equal or less than 0.05. It is noteworthy that almost 25% identified proteins were from Arabidopsis Thaliana proteome. We have removed all these proteins form the list of proteins in Appendix A to reduce complexity of the data. Many of these proteins may be either homologous to rat proteins or related to food proteins that could get into the collection tubes due to the design of the metabolic cages used in the study. It can be seen from column 2 (Control 0h vs. serine 0h) that there are a lot of false positive changes for many proteins. We believe it is due to inconsistent sample handling like multiple freeze-thaw cycles and storage. The samples were stored for more than 3 years before the analysis. The samples were also collected on different days. This clearly illustrates the great importance of consistency among samples. Nevertheless many occurring changes can be identified.

Clusterin was reported as a biomarker in many toxicological as well as cancer studies (Rithidech et al., 2009; Partheen et al., 2008; Alexopoulos et al., 2008; Yang et al., 2007; Rached et al., 2008; Nakamura et al., 2006). Many of the reported investigations are related to kidney toxicity. In our study we have found clusterin level was elevated 3 to 5-fold. It is not clear at this point whether the protein can serve as a reliable indicator (biomarker) of a certain condition.

Citrate synthetase exhibited the most significant changes in our D-serine toxicity label free study. It showed up to 40 fold increase in the protein level. The protein is highlighted in green color in Appendix C.

Beta-2-microglobulin was elevated on average two-fold. We have found this protein in 2D DIGE based D-serine toxicity study described in 2.1.1.1. It appears that fold change of this protein is very close when it compared between two different proteomic (2D DIGE and label free) approaches.

3.1.1.3 Conclusions on D-serine toxicity assessed by proteomic approaches

Overall, many of proteins showed dramatic changes in the D-serine toxicity study. One of most interesting new potential biomarkers is hornerin. It is becoming clear that the best approach would be to generate a panel of potential biomarkers, since it appears that levels of many proteins undergo quite dramatic changes under different disease conditions. A panel of specific biomarkers could address the identification of certain conditions more precisely. To create such a panel for kidney toxicity, studies using several other kidney toxicants must be completed. Many of the proteins reported here require further validation using other approaches such as enzyme-linked immunosorbent assays (ELISAs) and Western blots.

3.1.2 Puromycin toxicity assessment

3.1.2.1 Puromycin toxicity assessment using 2D DIGE

Rats given puromycin aminonucleoside develop transient visceral epithelial cell injury accompanied by heavy proteinuria (Vernier et al., 1959; Ryan et al., 1975). Rat's kidneys that recover from acute puromycin nephrosis later develop widespread glomerular and tubulointerstitial injury. Initial recovery form nephrosis is followed by late development of segmental glomerular sclerosis independent of any further administration of puromycin (Anderson et al., 1988). Persistent tubulointerstitial changes including interstitial edema, focal tubular atrophy and dilation, and infiltration of inflammatory cells have been identified during the recovery phase (Glasser et al., 1977; Eddy et al., 1988; Diamond et al., 1990). Main aim of our study was to identify biomarkers that indicate early stages of kidney injury by puromycin.

Nine animals, three time points, 0, 24 and 48 hr, and three doses, 0, 75 and 150 mg/kg, were used for urine collections for puromycin toxicity study (Table 6).

Table 6: Dosages and time points of rats urine samples used in puromycin toxicity study

Treatment dosage, mg/kg	Rat #	0 hr	24 hr	48 hr
0	301	301A	301B	301C
	302	302A	302B	302C
	303	303A	303B	303C
75	313	313A	313B	313C
	314	314A	314B	314C
	315	314A	314B	315C
150	316	315A	315B	316C
	317	317A	317B	317C
	318	318A	318B	318C

301 through 318 are assigned numbers of animals used in puromycin toxicity study. Animals 301-303, 313-315 and 316-318 were dosed with saline, 75mg/kg and 150mg/kg of puromycin respectively. A, B and C are 0 hr, 24 hr and 48 hr sampling points, respectively.

All procedures were exactly the same as described in 2.1.1. The only minor difference was the use of 30 ug of protein for labeling with Cy dyes instead of 50ug of protein used in D-Serine toxicity study. 120 ug total protein was used to load on each IEF strip and 2D gel, respectively. Sample composition for each strip/gel is shown in Table 7.

Table 7: Experimental design of sample composition for each strip/gel used in puromycin toxicity study

Gel #	Cy2	Cy3	Cy5
1	30ug IS	30 ug 301A	30 ug 301C
2	30 ug IS	30 ug 316B	30 ug 302A
3	30 ug IS	30 ug 313C	30 ug 302C
4	30 ug IS	30 ug 301B	30 ug 303A
5	30 ug IS	30 ug 317A	30 ug 303B
6	30 ug IS	30 ug 314A	30 ug 313A
7	30 ug IS	30 ug 317C	30 ug 313B
8	30 ug IS	30 ug 314B	30 ug 314C
9	30 ug IS	30 ug 318A	30 ug 315B
10	30 ug IS	30 ug 302B	30 ug 316A
11	30 ug IS	30 ug 315A	30 ug 316C
12	30 ug IS	30 ug 318B	30 ug 317B
13	30 ug IS	30 ug 303C	30 ug 318C
14	30 ug IS	30 ug 315C	

Sample composition for each gel is shown in the Table. 120 ug of total protein after IEF separation was loaded on each gel. Internal standards, controls and samples from dosed animals were labeled with Cy 2, 3 and 5, respectively. 301 through 318 are assigned numbers of animals used in puromycin toxicity study. A, B and C are 0 hr, 24 hr and 48 hr sampling points, respectively.

After all gel images were analyzed with Decyder Software 6.5 (Amersham) internal standard (IS) image with largest number of spots (Gel #7 Cy2 image) was chosen as a master gel. All images were matched and normalized by master gel image. The master gel image is shown in Figure 11.

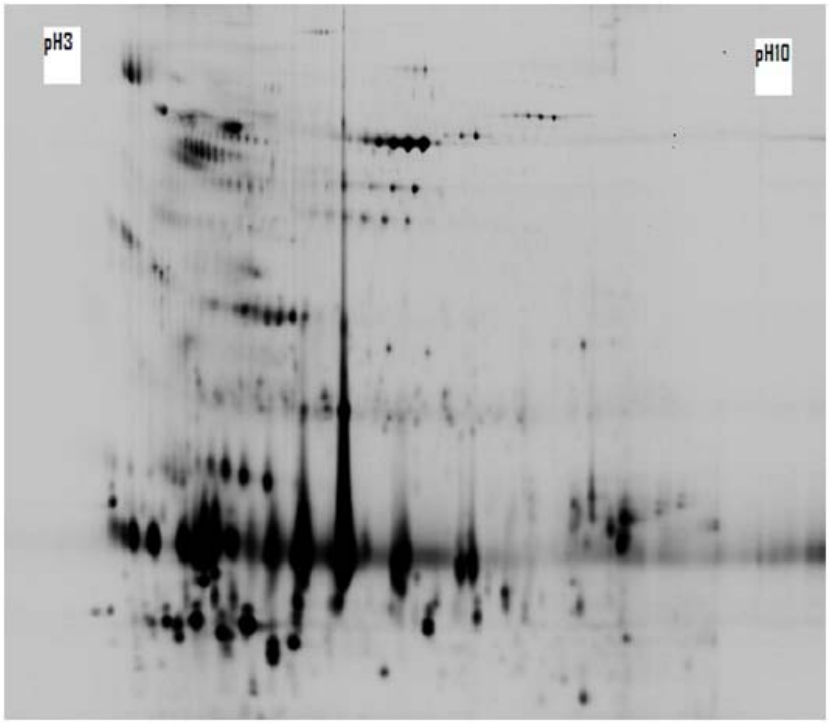


Figure 11: Internal standard Cy2 image of gel #7 chosen as master gel for data analysis
The gel was chosen as a master gel (reference gel) for subsequent data analysis of all gel images.

The Two-Way ANOVA was performed to determine the significant differences between proteins expressions based on dose and time of urine collection after the treatment with puromycin:

1. 0 mg vs. 75 mg
2. 75 mg vs. 150 mg
3. 0 mg vs. 150 mg
4. 0 hr vs. 24 hr
5. 0 hr vs. 48 hr
6. 24 hr vs. 48 hr

After all the images were analyzed, we filtered the data by average ratio value (only data spots that showed difference ≥1.5 or ≤1.5 fold change were included) and p-values (only $p \leq 0.05$ are included). Significantly different spots were distinguished using 2 Way ANOVA analyses. The results of the analysis are shown in Table 8. Average ratio changes for the spots that are significantly different by both time and dose are shown in Table 9. Four identified spots are shown in Figure 12. Spot 346 appeared to be differently expressed in every comparison. The spot is highlighted in yellow color in Table 9.

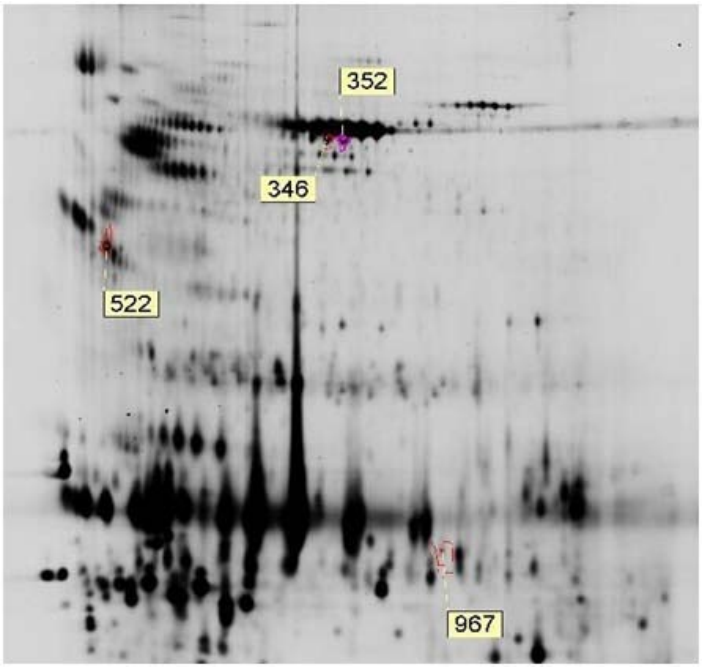


Figure 12: Protein spots showing significant difference after two condition data analysis, time and dose

0 hr 150 mg vs. 48 hr 150 mg, Gel #7, Cy3 image, Rat # 317 were compared in this figure.

Table 8: Number of significantly different spots indentified by 2-Way ANOVA with time and dose parameters

	Number of significantly different spots by		
Comparison	Both parameters	Dose only	Time only
24 hr vs. 0 hr	3	3	43
48 hr vs. 24 hr	2	2	48
48 hr vs. 0 hr	3	3	81
75 mg vs. 0 mg	3	5	9
150 mg vs. 0 mg	4	7	42
150 mg vs. 75 mg	3	6	41

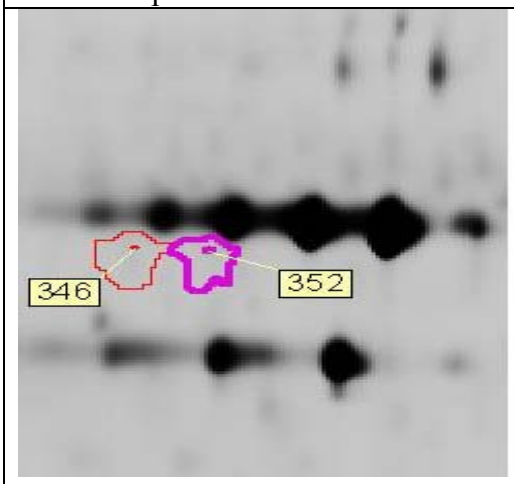
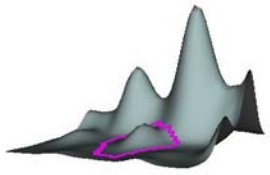
The table shows number of significantly different spots identified employing 2-Way ANOVA analysis for dose, time and both parameters.

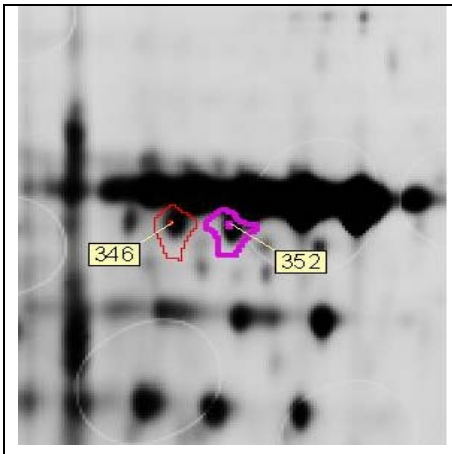
Table 9: Average ratios for significantly different spots by time and dose

Protein # on Master gel	75 mg vs. 0 mg	150 mg vs. 75 mg	150 mg vs. 0 mg	24 hr vs. 0 hr	48hr vs. 24 hr	48 hr vs. 0 hr
967	-1.7		-1.96			
522		4.12	3.09	3.44	-2.02	1.71
346	-1.72	7.45	4.33	3.44	1.55	5.34
352	-1.88	7.13	3.78	3.91		5.05

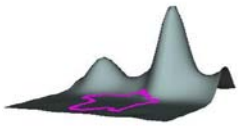
Four significantly different spots identified by 2-Way ANOVA are shown. These four spots are significantly different in relation to at least one of the conditions – time and dose. Number of the protein corresponds to the spot number on the Master Gel. Negative and positive fold changes are shown. Spot 346 is differently expressed in relation to both conditions – time and dose.

Examples of graphical views for protein spots 346, 352 and 522 are shown in Figure 13.

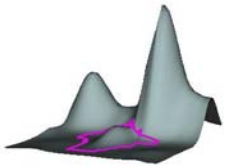
2D Gel representation	3D representation
 Gel #10Cy5 150 mg treatment 0 hr Rat #316	 #346 at the time 0 hr  #346 at the time 48 hr



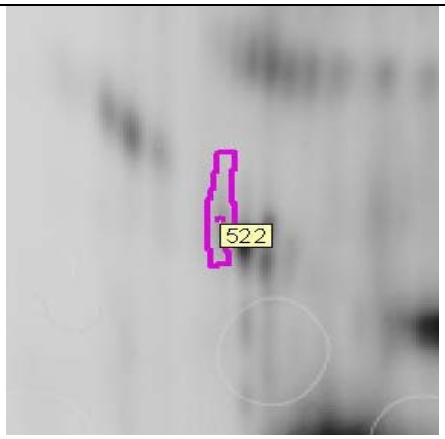
Gel #11 Cy5 150 mg treatment 48 hr Rat #316



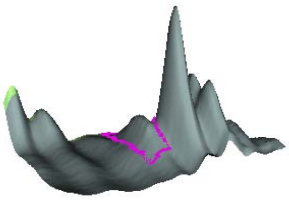
#352 at the time 0 hr



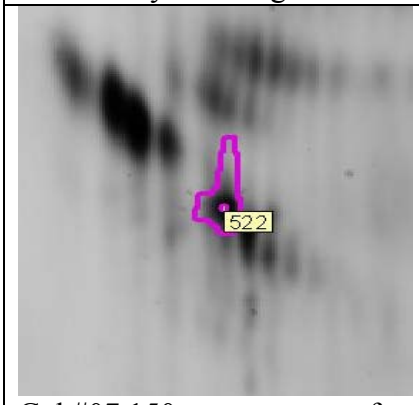
#352 at the time 48 hr



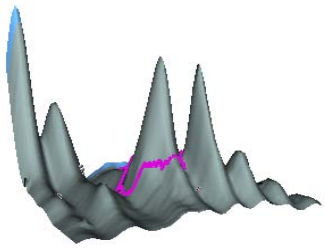
Gel# 05 Cy5 150 mg treatment 0 hr Rat# 317



522 at the time 0 hr



Gel #07 150mg treatment after 48 hr Rat #317



522 at the time 48 hr

Figure 13: Gel and Graphical views for protein spots 346, 322, and 522

Graphical views for protein spots 346, 352 and 522 are shown. Animal numbers, gel numbers, time and dose after the exposure to puromycin are shown. Left panel and right panel represent 2D and three dimensional (3D) views, respectively.

Spots 346, 352, 522 and 967 were cored out from preparative gel and subjected to the identification procedure described in [sections 1.1.1.2 and 1.1.1.3 of the current Tech Report]. Identifications of the proteins from the above mentioned spots did not reveal any interesting proteins (Data is not shown). All of the spots turned out to be keratins.

3.1.2.2 Conclusions on puromycin toxicity assessed by 2D DIGE

2D DIGE approach to assess puromycin toxicity in rat urines did not reveal any new potential biomarkers. The changes we observed for keratins might be very specific. It is very possible that these proteins undergo very specific post translational modifications. Further investigations may reveal what types of modifications occur in keratins at 24/48 hour intervals after exposure of animals to puromycin. These modifications might be extremely specific for certain conditions. We would also like to note that conditions of the animal experiment may not be favorable for biomarker discovery via proteomic study. Most published studies related to the kidney toxicity after puromycin exposure find changes in 5-15 days after the exposure (Anderson et al., 1988). It was suggested that visceral epithelial cells were the major targets of puromycin toxicity in the kidney. Damage to these cells does not cause huge changes except proteinuria which we also observed in the forms of keratins. Several published studies have suggested that visceral epithelial cells cannot be replaced (Fries et al., 1989; Nagata et al., 1992). It can explain why more severe damage occurs after 10-20 days after the exposure to puromycin aminonucleoside. In our case we were looking for changes that occur in 2 days. That might be too short time for changes to show up. Our goal was to discover the most sensitive biomarkers that reflect minor changes to even low concentrations of toxicants. We speculate that short exposure along with lower than usual concentrations of puromycin have rendered this experiment to be not fully successful.

3.2 Metabonomics

3.2.1 D-serine toxicity assessment

3.2.1.1 D-serine toxicity assessment

Male Fischer 344 rats (Charles River Laboratories, Wilmington, MA) weighing 222-258 g at the beginning of the study were caged in metabolic cages for the collection of urine. Treated animals were given a single intraperitineal injection of D-serine in saline. Control animals received an injection of vehicle only (0.9% saline). All animal procedures were conducted in accordance with the Guide for the Care and Use of laboratory Animals, National Research Council, 1996, and the Animal Welfare Act of 1966, as amended. Urine was collected into tubes containing 1 ml of 1% sodium azide to control bacterial growth. The urine was stored at -20°C until processed. Treated animals received 5, 20, or 500 mg/kg D-serine. Urine was collected at five twenty-four hour intervals (0 hr, 24 hr, 48 hr, 72 hr, and 96 hr post-dosing). Animals/samples used in the study are shown in Table 10.

Table 10: Animals/samples used in study

Animal #	Time point (hr)	Dose (mg/kg)	Animal #	Time point (hr)	Dose (mg/kg)	Animal #	Time point (hr)	Dose (mg/kg)
242	0	0	248	72	500	265	24	20
242	24	0	248	96	500	265	48	20
242	48	0	249	0	500	265	72	20
242	72	0	249	24	500	265	96	20
242	96	0	249	48	500	266	0	20
243	0	0	249	72	500	266	24	20
243	24	0	249	96	500	266	48	20
243	48	0	250	0	500	266	72	20
243	72	0	250	24	500	266	96	20
243	96	0	250	48	500	267	0	5
244	0	0	250	72	500	267	24	5
244	24	0	250	96	500	267	48	5
244	48	0	251	0	500	267	72	5
244	72	0	251	24	500	267	96	5
244	96	0	251	48	500	268	0	5
245	0	0	251	72	500	268	24	5
245	24	0	251	96	500	268	48	5
245	48	0	262	0	20	268	72	5
245	72	0	262	24	20	268	96	5
245	96	0	262	48	20	269	0	5
246	0	0	262	72	20	269	24	5
246	24	0	262	96	20	269	48	5
246	48	0	263	0	20	269	72	5
246	72	0	263	24	20	269	96	5
246	96	0	263	48	20	270	0	5
247	0	500	263	72	20	270	24	5
247	24	500	263	96	20	270	48	5
247	48	500	264	0	20	270	72	5
247	72	500	264	24	20	270	96	5
247	96	500	264	48	20	271	0	5
248	0	500	264	72	20	271	24	5
248	24	500	264	96	20	271	48	5
248	48	500	265	0	20	271	72	5
						271	96	5

Samples for D-Serine LC/MS metabonomic study were from animals 242 through 248. Doses and sampling time points are shown in the Table.

LC/MS-based urine analysis revealed numerous metabolic changes in the urine of animals after D-serine treatment compared to control animals. More than 4000 peaks were

registered and matched after LC/MS data was analyzed with the in-house software. It would be appropriate to note that many peaks may represent different forms of the same metabolite. These modifications may include water loss as well as different adducts. Adducts can be metal ions like Na^{+} and K^{+2}, acetyl, formyl and others. Besides that, complete list includes monoisotopic peaks in many cases as well. A heat map of all registered peaks is shown in Figure 14.

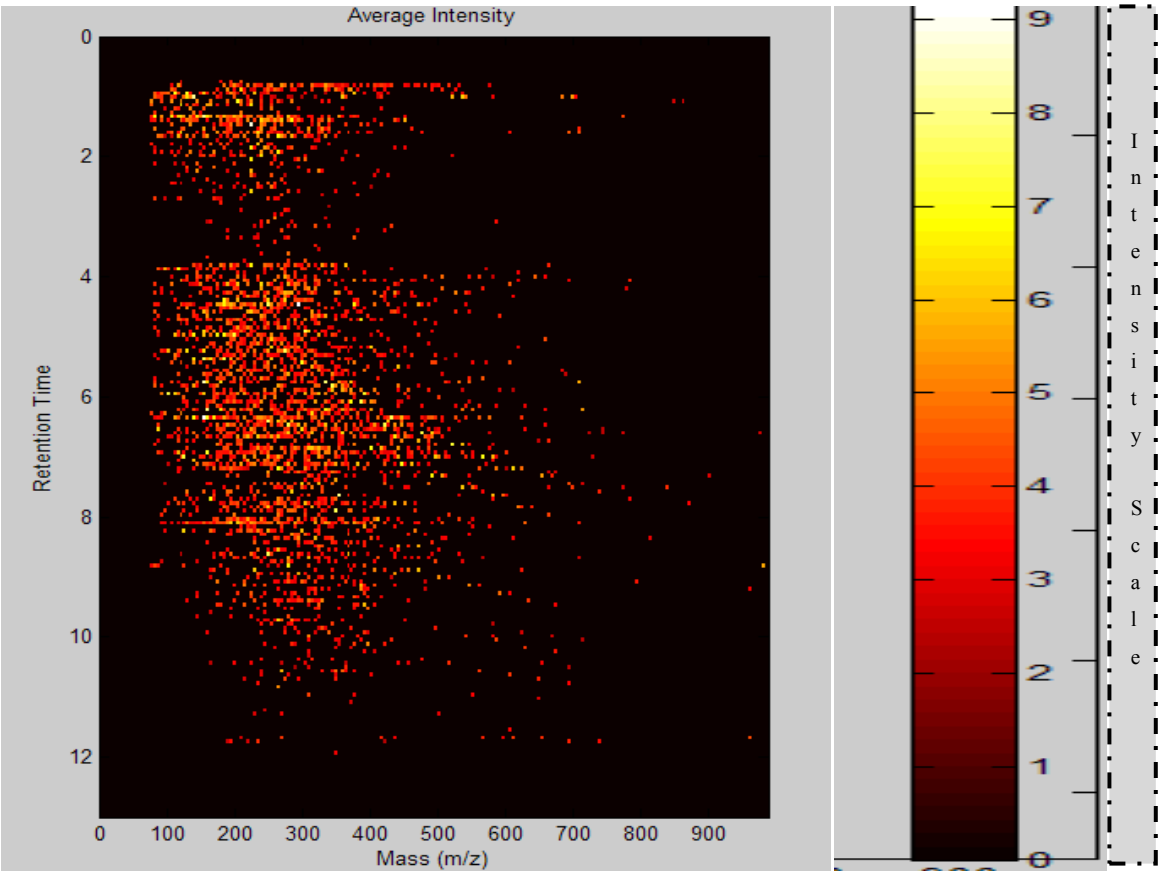
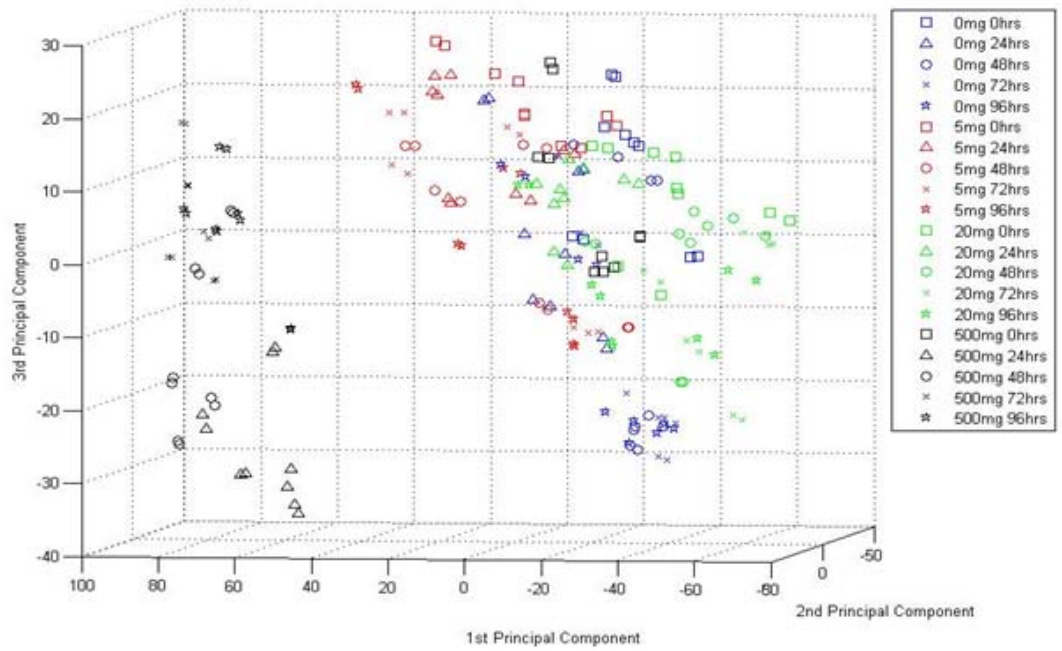


Figure 14: Heat map of all peaks registered and matched by in-house software
Brighter color reflects higher intensities of the peaks.

The principal component analysis (PCA) performed for all groups of animals is shown in Figure 15. It shows clear separation between sample groups. 500 mg/kg dose shows the most dramatic separation for all time points except 500 mg/kg dose at 0 hr that is grouped together with other sample groups especially 0 mg/kg and 5 mg/kg. For 500 mg/kg dose it appears that PCA analysis clearly indicates more similarities between 24 hr and 48 hr time point groups, as well as 72 hr and 96 hr time point groups after the D-serine uptake. Since PCA plot for all groups is very busy, we graphed another PCA plot where we included data for 0, 5, 20 and 500 mg/kg doses at 24 hours only (Figure 15B).

A



B

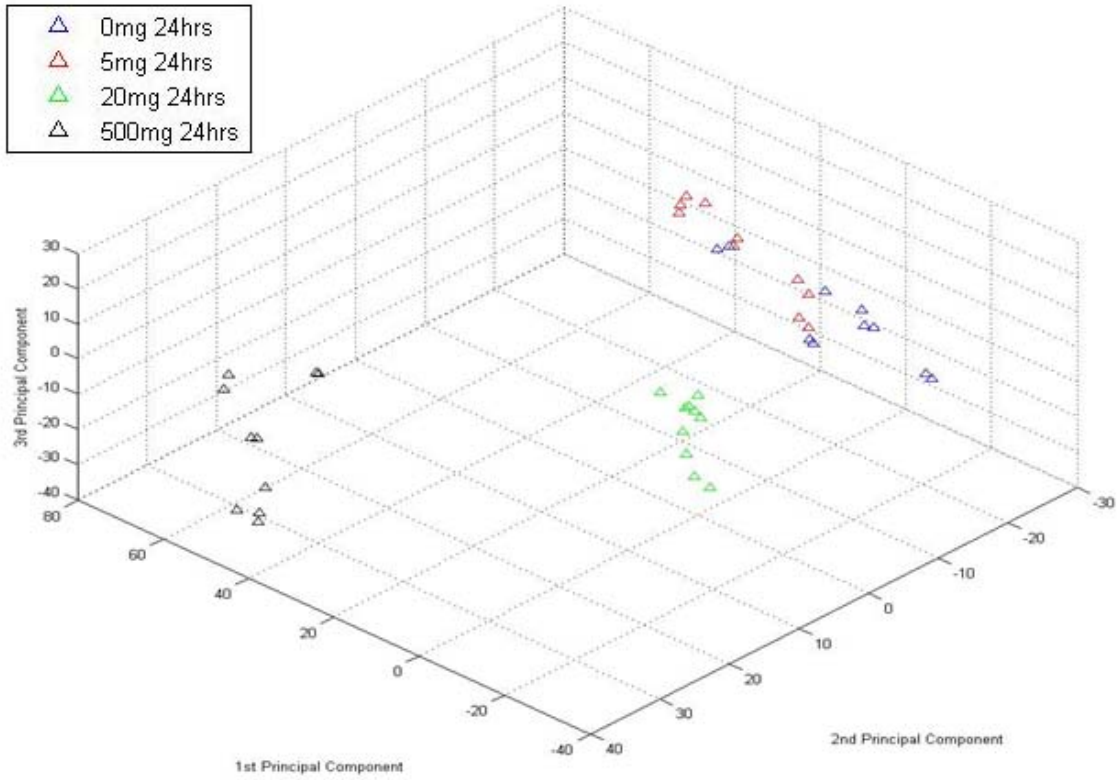


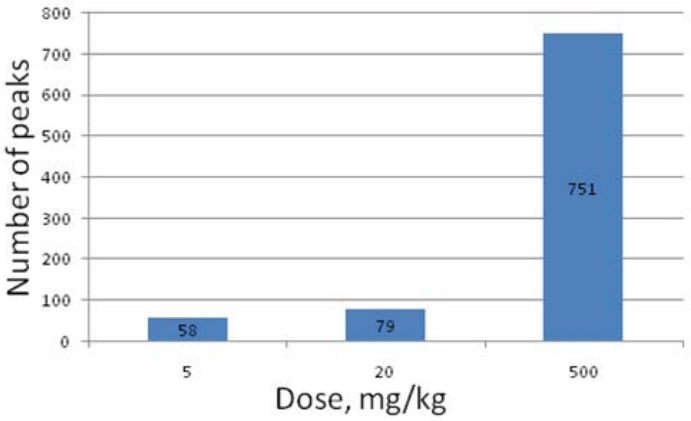
Figure 15: Principal component analysis of LC/MS data

A - Principal component analysis of LC/MS data for all experimental animal groups of the study. Legend is in the right corner of the figure. B - Principal component analysis of LC/MS data for 0, 5, 20 and 500 mg/kg doses at 24 hours only. Legend is in the lower left corner of the figure.

The doses of 500 mg/kg caused the most significant changes when compared to other doses, 5 and 20 mg/kg (Figure 16A). Most metabonomic changes in urine were observed at 24 hr, 48 hr and 72 hr after treatment with 500 mg/kg D-serine (Figure 16B).

Changes at 72 hours are not as dramatic as at 24 and 48 hr. However the changes at 72 hr are significant. The number of peaks that undergo at least a 2-fold change is almost 13 times higher for the 500 mg/kg dose than the 5 mg/kg dose. It is interesting to mention that the most dramatic changes occur around 24 hours after the exposure resulting in the greatest fold-changes for the most metabolites at 24 and 48 hours. The changes literally disappear at 96 hours, which most likely indicates kidney recovery.

A



B

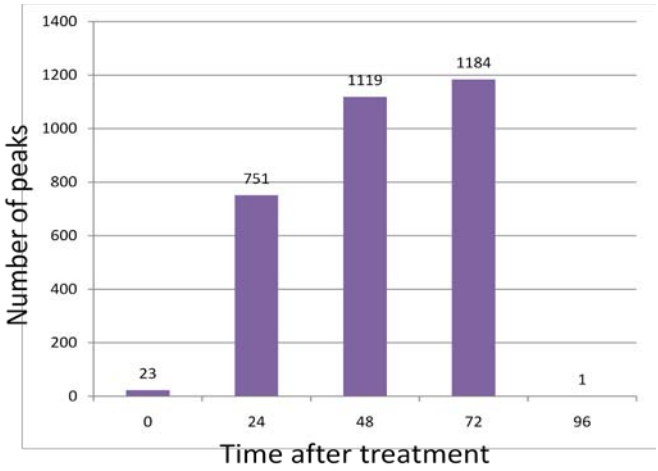


Figure 16: The number of identified peaks that exhibit greater than 2-fold intensity change
A – The number of identified peaks that exhibit greater than 2-fold intensity change at different treatment doses with D-serine. B – The number of identified peaks that exhibit at least 2-fold intensity change at 500 mg/kg treatment for different time points. The minimum intensity threshold for peaks was set to 40. Isotopic peaks are excluded.

At 24 hours post-dosing for the 500 mg/kg group, as many as 426 peaks show a greater than 2-fold change with the peak intensity cut-off set to a minimum of 100 (Figure 17). Five metabolite peaks exceeded 100-fold change with the same intensity threshold.

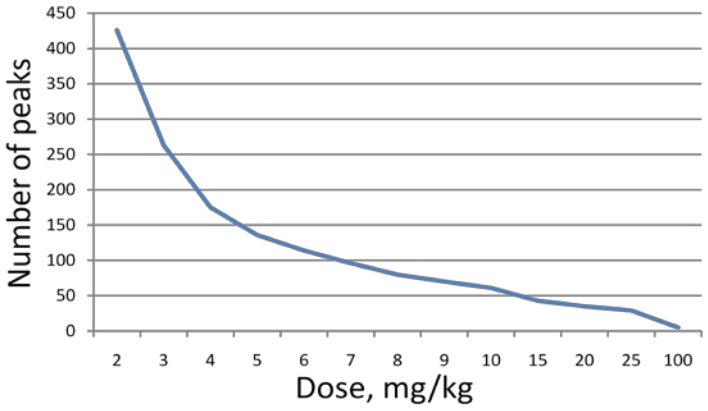


Figure 17: The number of identified peaks versus absolute fold-change at 500 mg/kg, 24 hours after treatment

The minimum intensity threshold for peaks was set to 100. Isotopic peaks are excluded.

Notably, a number of peaks exhibit statistically significant changes, while their intensities are relatively low. Most of those peaks in our data analysis demonstrate negative changes. We have excluded isotopic peaks in our data analysis. However, some percentage of differentiated peaks can be attributed to adduct acquisition by metabolites as well as water loss. Thus, the difference of 18 mass units between peaks 1569 and 1598; 952 and 246; 1642 and 1532; 1697 and 1664; and 3277 and 42 strongly suggest a water loss. Each set of ions elutes from the column at the same time of 4.2, 3.9, 6.2, 7.1 or 4.5 minutes, respectively. We included metabolite #3 in Figure 18 to demonstrate a metabolite that most likely is related to food or environment. The dose dependent effect can be clearly seen for the metabolite.

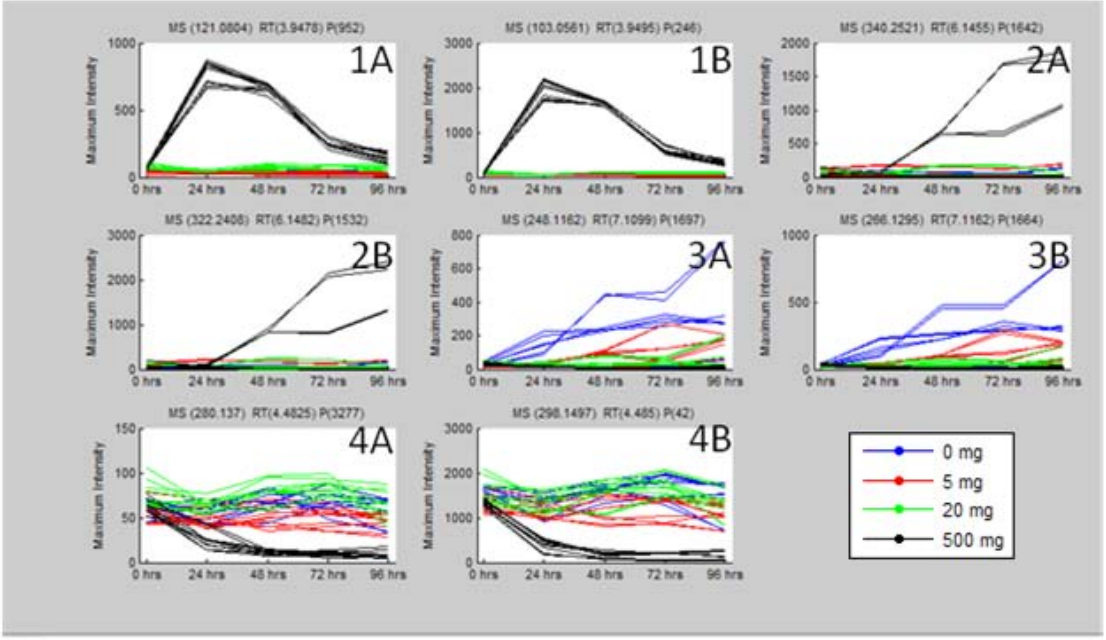


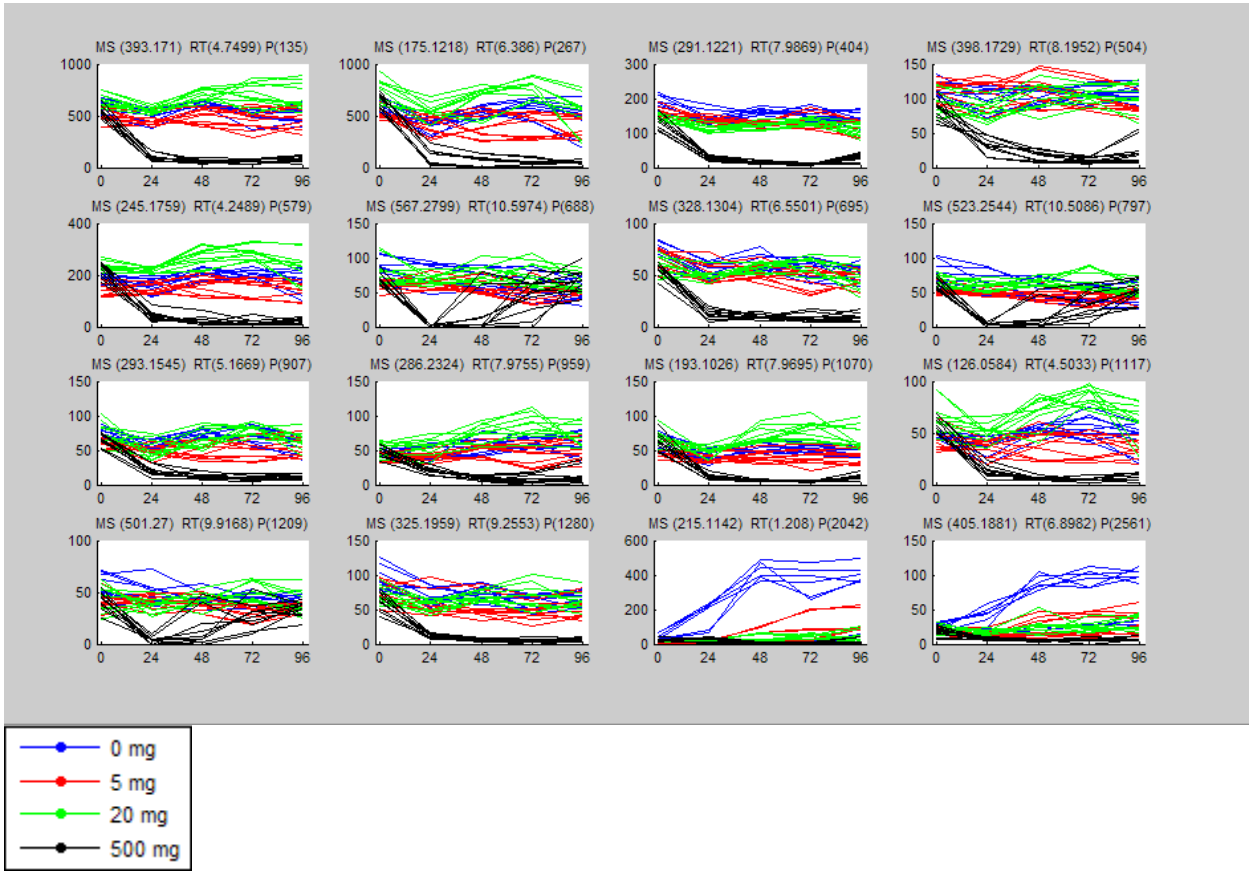
Figure 18: Water loss observed for metabolites

A - original metabolites. B - presumably same metabolites after loss of water. Masses and retention times of the metabolites are above the plots. Legend for the plots is in the right lower corner.

Lists of potential metabolites that exhibit at least 2-fold increase or decrease in intensity after 500 mg/kg dose of D-serine, at 24 hours are shown in Appendices B and C, respectively.

Examples of selected peak plots of negative (A) and positive (B) changes after 500 mg/kg D-serine exposure at 24 hours are shown in Figure 19.

A


MS (393.171) RT(4.7499) P(135)
MS (175.1218) RT(6.386) P(267)
MS (291.1221) RT(7.9869) P(404)
MS (398.1729) RT(8.1952) P(504)
MS (245.1759) RT(4.2489) P(579)
MS (567.2799) RT(10.5974) P(688)
MS (328.1304) RT(6.5501) P(695)
MS (523.2544) RT(10.5086) P(797)
MS (293.1545) RT(5.1669) P(907)
MS (286.2324) RT(7.9755) P(959)
MS (193.1026) RT(7.9695) P(1070)
MS (126.0584) RT(4.5033) P(1117)
MS (501.27) RT(9.9168) P(1209)
MS (325.1959) RT(9.2553) P(1280)
MS (215.1142) RT(1.208) P(2042)
MS (405.1881) RT(6.8982) P(2561)
0 mg
5 mg
20 mg
500 mg

B

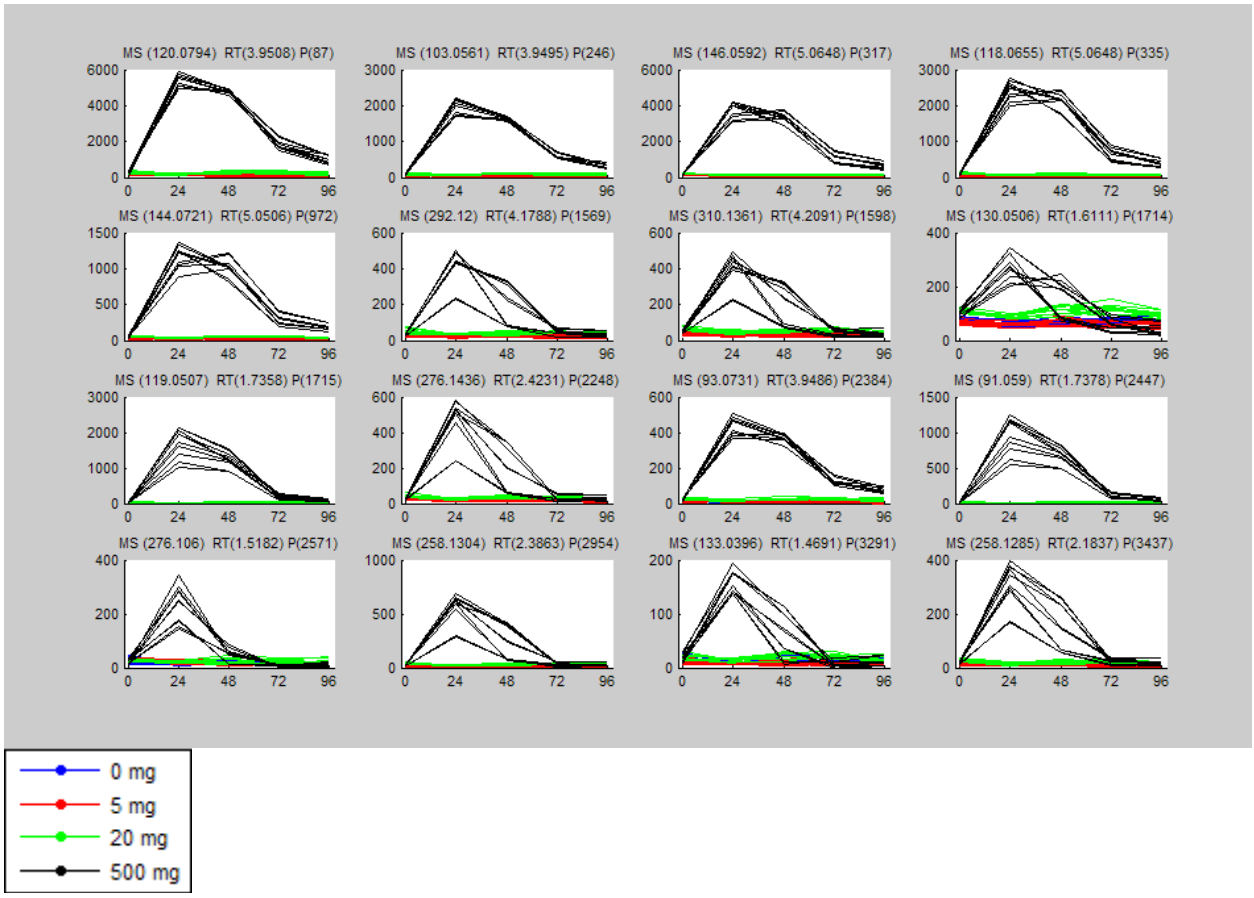


Figure 19: Examples of selected peak plots

Negative (A) and positive (B) changes after 500 mg/kg D-serine exposure, 24 hr. Legends are in the left lower corners.

An example of identified metabolite is shown in Figure 20. Purchased metabolite standard was run under the same LC conditions followed by MS/MS as selected samples. Matching retention time and MS/MS fragmentation data almost certainly indicate the identification of the metabolite. In our study a metabolite with m/z 176.09 and retention time 8.287 min suggested that it could be 3-Indolylacetic acid. The metabolite showed over two-fold decrease after 500 mg/kg D-serine treatment at 24 hr (the metabolite is highlighted in green color in Appendix C). MS/MS spectra of 3-Indolylacetic acid along with spectra from rat urine samples are shown in Figure 20A. Not normalized (Figure 20B) and normalized (Figure 20C) plots show changes for 3-Indolylacetic acid throughout the course of D-serine study.

A

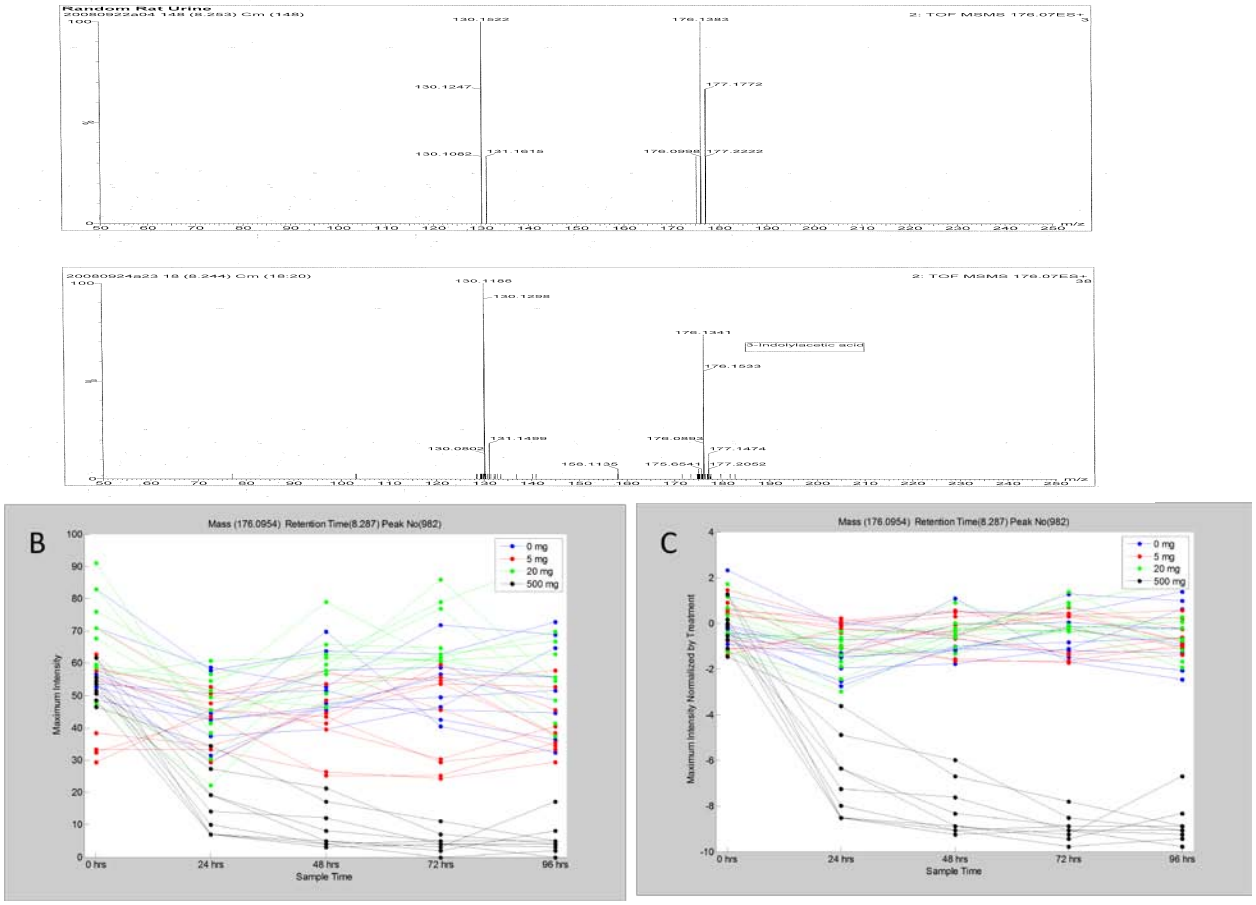


Figure 20: Identification of selected metabolites

Retention times and MS/MS fragmentation of 3-Indolylacetic acid is shown for standards along with corresponding MS/MS from D-serine urine samples on A. Not normalized (B) and normalized (C) plots show changes for 3-Indolylacetic acid throughout the course of D-serine study.

3.2.1.2 Conclusions on D-serine toxicity assessed by metabonomic techniques

The data clearly demonstrates dramatic changes in the urinary metabolic profile in response to the kidney toxicant, D-serine. A list of potential metabolites corresponding to masses identified in urine of rats is presented. The presented metabolites show at least 10-fold absolute changes after the exposure of animals to D-serine. D-serine metabonomic profiling demonstrates that most changes occur between 24-72 hours. The most dramatic changes occur at the 24 hour time point after exposure to 500 mg/kg D-serine. It appears from the data that near-normal kidney function resumes at 96 hours. Most of metabolites corresponding to selected peaks can be identified. The metabolite with m/z 176.09 and retention time 8.287 min showed over two-fold decrease after 500 mg/kg D-serine treatment at 24 hr. After commercial standard was run we confirmed the metabolite identity, as 3-Indolylacetic acid.

4. REFERENCES

Alexopoulos EC, Cominos X, Trougakos IP, Lourda M, Gonos ES, Makropoulos V: Biological Monitoring of Hexavalent Chromium and Serum Levels of the Senescence Biomarker Apolipoprotein j/Clusterin in Welders. Bioinorg Chem 2008, Appl: 420578.

Anderson S, Diamond JR, Karnovsky MJ, Brenner BM: Mechanisms Underlying Transiton from Acute Glomerular Injury to Late Glomerular Sclerosis in Rat Model of Nephrotic Syndrome. J Clin Invest 19888, **82**: 1757-1768.

Askew DJ, Silverman GA: Intracellular and Extracellular Serpins Modulate Lung Disease. J Perinatol 2008, **28**(Suppl 3): S127-135.

Brouwer A, van der Berg KJ: Binding of a Metabolite of 3,4,3',4'-tetrachlorobiphenyl to Transthyretin Reduces Serum Vitamin ATransport by Inhibiting the Formation of the Protein Complex Carrying Both Retinol and Thyroxin. Toxicol Appl Pharmacol 1986, **85**(3): 301-312.

Diamond JR, Anderson S: Irreversible Tubulointerstitial Damage Associated with Chronic Aminonucleoside Nephrosis. Amelioration by Angiotensin I Coverting Enzyme Inhibition. Am J Pathol 1990, **137**:1323-1332.

Eddy AA, Michael AF: Acute Tubulointerstitial Nephritis Associated with Aminonucleoside Nephrosis. Kidney Int 1988, **33**: 14-23.

Ferguson MA, Vaidya VS, Bonventre JV: Biomarkers of Nephrotoxic Acute Kidney Injury. Toxicol 2008, **245:** 182-193.

Fries JW, Sadstrom DJ, Meyer TW, Rennke HG: Glomerural Hypertrophy and Epithelial Cell Injury Modulate Progressive Glomerulosclerosis in the Rats. Lag Invest 1989, **60**: 205-218.

Ganote CE, Peterson DR, Carone FA: The Nature of D-serine-Induced Nephrotoxicity. Am J Pathol 1974, **77**: 269-282.

Genomics Institute of the Novartis Research Foundation. Database on gene function and structure. http://biogps.gnf.org.

Glasser RJ, Velosa JA, Michael AF: Experimental Model of Focal Sclerosis. 1. Relationship to Protein Excretion in Aminonucleoside Nephrosis. Lab Invest 1977, **36**: 519-526.

Huber M, Siegenthaler G, Mirancea N, Marenholz I, Nizetic D, Breitkreutz D, Mischke D, Hohl D: Isolation and Characterization of Human Repetin, a Member of the Fused Gene Family of the Epidermal Differentiation Complex. J Invest Dermatol 2005, **124**(5): 998-1007.

Lee SC, Kim IG, Marekov LN, O'Keefe EJ, Parry DA, and Steinert PM: The Structure of Human Trichohyalin. Potential Multiple Roles as a Functional EF-hand-like Calcium-binding Protein, a Cornified Cell Envelope Precursor, and an Intermediate Filament-associated (Cross-linking) Protein. J Biol Chem 1993, **268:** 12164–12176.

Machado FR, Silva E: Coagulation and sepsis. Endocr Metab Immune Disord Drug Targets 2006, **6**(2): 175-182.

Makino T, Takaishi M, Morohashi M, Huh NH: Hornerin, a Novel Profilaggrin-like Protein and Differentiation-specific Marker Isolated from Mouse Skin. J Biol Chem 2001, **276**(50): 47445-47452.

Meier U, Gressner O, Lammert F, Gressner AM: Gc-Globulin: Roles in Response to Injury. Clin Chem 2006, **52**(7): 1247-1253.

Meistermann H, Norris JL, Aernis H-R, Cornett DS, Friedlein A, Erskine AR, Augustin A, De Vera Mudry MC, Ruepp S, Suter L, Langen H, Caprioli RM, Ducrett A: Biomarker Discovery by Imaging Mass Spectrometry. Molecular & Cellular Proteomics 2006, **5:** 1876-1886.

Nagata M, Kriz W: Glomerural Damage after Uninephroctomy in Young Rats. II. Mechanical Stress on Podocytes as a Pathway to Sclerosis. Kidney Int 1992, **42**: 148-160.

Nakamura E, Abreu-e-Lima P, Awakura Y, Inoue T, Kamoto T, Ogawa O, Kotani H, Manabe T, Zhang GJ, Kondo K, Nosé V, Kaelin WG Jr: Clusterin is a Secreted Marker for a Hypoxia-Inducible Factor-Independent Function of the von Hippel-Lindau Tumor Suppressor Protein. Am J Pathol 2006, **168**(2): 574-84.

O'Reilly MS: Antiangiogenic Antithrombin. Semin Thromb Hemost 2007, **33**(7): 660-666.

Partheen K, Levan K, Osterberg L, Claesson I, Fallenius G, Sundfeldt K, Horvath G: Four Potential Biomarkers as Prognostic Factors in Stage III Serous Ovarian Adenocarcinomas. Int J Cancer 2008, **123**(9): 2130-2137.

Ragg H: The Role of Serpins in the Surveillance of the Secretory Pathway. Cell Mol Life Sci 2007, **64**(21): 2763-2770.

Rached E, Hoffmann D, Blumbach K, Weber K, Dekant W, Mally A: Evaluation of Putative Biomarkers of Nephrotoxicity after Exposure to Ochratoxin in Vivo and in Vitro. Toxicol Sci 2008, **103**(2): 371-381.

Rithidech K, Honikel L, Milazzo M, Madigan D, Troxell R, Krupp L: Protein Expression Profiles in Pediatric Multiple Sclerosis. Potential Biomarkers. Mult Scler 2009, **15**(4): 455-464.

Ryan GB, Karnovsky MJ: An Ultrastructural Study of the Mechanisms of Proteinuria in Aminonucleoside nephrosis. Kidney Int 1975, **8**: 219-232.

Saraiva MJ, Costa PP, Birken S, Goodman DS: Presence of an Abnormal Tranthyretin (Prealbumin) in Portuguese Patients with Familial Amymoidotic Polyneuropathy. Trans Assoc Am Physicians 1983, **96**: 261-270.

Staus DS: Nutritional Regulation of Visceral Markers in Rat Liver and Cultured Hepatoma Cells. Clin Chem Lab Med 2002, **40**(12): 1274-1280.

Vernier RL, Papermaster BW, Good RA: Aminonucleoside Nephrosis: 1. Electron microscopic study of the renal leson in rats. L Exp Med 1959, **109**: 115-126.

Wu ZH, Meyer-Hoffert U, Bartels J, He YH, Schroder J-M: Antimicrobially Active Hornerin Peptides as Protective Factors of Healthy Skin. 37th Annual Meeting of the European Society for Dermatological Research, 5-8 September 2007, Zurich, Switzerland.

Yang A, Trajkovic D, Illanes O, Ramiro-Ibáñez F: Clinicopathological and Tissue Indicators of para-Aminophenol Nephrotoxicity in Sprague-Dawley Rats. Toxicol Pathol. 2007, **35**(4): 521-532.

Zorio E, Gilabert-Estellés J, España F, Ramón LA, Cosín R, Estellés A: Fibrinolysis: the Key to New Pathogenetic Mechanisms. Curr Med Chem 2008, **15**(9): 923-929.

LIST OF SYMBOLS, ABBREVIATIONS, AND ACRONYMS

2D - two dimensional
2D DIGE – two dimensional difference in-gel electrophoresis
3D - three dimensional
ANOVA – analysis of variance
BVA – Biological Variation Analysis
CHAPS - 3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate
DAPI - 4′,6-Diamidino-2-phenyindole
DIA - differential in-gel analysis
DIGE - difference in-gel electrophoresis
DTT – dithiothreitol
ELISA – enzyme-linked immunosorbent assay
ESI – electrospray ionization
eV – electronvolt/electronvolts
g - gram
GSC – group specific component protein
HLP – hornerin-like protein
HPW – Human Performance Wing
hr – hour/hours
IEF - isoelectric focusing
IPG – immobilized pH gradient
IS – internal standard
kg – kilogram/kilograms
LC – liquid chromatography
LC/MS – liquid chromatography coupled mass spectrometry
LC/MS/MS - liquid chromatography coupled tandem mass spectrometry
m/z – mass over charge
M - Molar
mg – milligram
min – minute/minutes
mM – milliMolar
MS – mass spectrometry
MS2 – tandem spectrometry (same as MS/MS), data-dependent fragmentation
MS/MS – tandem mass spectrometry (same as MS2), data-dependent fragmentation
PAGE – polyacrylamide gel electrophoresis
RHBP – Biotechnology Branch, Biosciences and Protection Division
s – second/seconds
SDS – sodium dodecyl sulfate
TFA – trifluoroacetic acid
ug – microgram/micrograms
ul – microliter/microliters
UPLC – ultrahigh performance liquid chromatography
V – volt/volts

APPENDIX A

Data analysis using Sieve software. Fold change is shown

	Control 24, 48 hr vs. D-serine 24, 48 hr	Control 0h vs. D-serine 0h	D-serine 0 hr vs. D-serine 24, 48 hr	D-serine 0, 24 hr vs. D-serine 48 hr	D-serine 24 hr vs. 48hr	Control 48 hr vs. D-serine 48 hr	D-serine 0 hr vs. D-serine 24 hr
10-formyltetrahydrofolate dehydrogenase - Rattus norvegicus (Rat)	10.46		7.789				8.911
130 kDa phosphatidylinositol 4,5-biphosphate-dependent ARF1 GTPase-activating protein - Rattus norvegicus (Rat)	4.993	0.474	2.043	0.402	1.269	6.17	1.047
14-3-3 protein epsilon - Rattus norvegicus (Rat)	4.554						
14-3-3 protein zeta/delta - Rattus norvegicus (Rat)	6.647		1.887		0.577		2.244
1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma 1 - Rattus norvegicus (Rat)				5.73	0.688		
2_-5_-oligoadenylate synthetase 1 - Rattus norvegicus (Rat)					0.669		
250 kDa substrate of Akt - Homo sapiens (Human)							
26S protease regulatory subunit 7 - Rattus norvegicus (Rat)	3.024				1.418		
26S proteasome non-ATPase regulatory subunit 1 - Rattus norvegicus (Rat)			3.124		0.598		4.577

26S proteasome regulatory subunit RPN2 - Candida glabrata (Yeast) (Torulopsis glabrata)			3.34				
28 kDa heat- and acid-stable phosphoprotein - Rattus norvegicus (Rat)				0.963			
2-amino-3-ketobutyrate coenzyme A ligase, mitochondrial precursor - Bos taurus (Bovine)							
2-hydroxyacylsphingosine 1-beta-galactosyltransferase precursor - Rattus norvegicus (Rat)	6.276				0.65		
2-oxoglutarate and iron-dependent oxygenase domain-containing protein 1 - Bos taurus (Bovine)	0.975		1.469	0.295	5.362	1.038	
2-oxoglutarate dehydrogenase E1 component, mitochondrial precursor - Caenorhabditis briggsae			1.637				
2-oxoglutarate dehydrogenase E1 component, mitochondrial precursor - Caenorhabditis elegans	1.631		2.85		0.891		
3-hydroxyisobutyryl-CoA hydrolase, mitochondrial precursor - Rattus norvegicus (Rat)					0.602		
3-isopropylmalate dehydratase - Candida maltosa (Yeast)	0.916	0.506	1.061				
4-aminobutyrate aminotransferase - Saccharomyces cerevisiae (Baker_s yeast)	4.668	0.894		0.874	0.715	1.337	

4F2 cell-surface antigen heavy chain - Rattus norvegicus (Rat)	0.545						
5_-nucleotidase precursor - Rattus norvegicus (Rat)		0.972					
5-hydroxytryptamine 2A receptor - Rattus norvegicus (Rat)					0.563		
60 kDa heat shock protein, mitochondrial precursor - Rattus norvegicus (Rat)	6.476		2.241	0.338	0.704	6.707	3.463
60S ribosomal protein L12 - Rattus norvegicus (Rat)	7.16	2.22	3.339		0.585		9.835
6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2 - Rattus norvegicus (Rat)	8.017				0.968	4.845	
6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 - Rattus norvegicus (Rat)					2.457		
6-phosphofructokinase type C - Rattus norvegicus (Rat)			2.408		0.554		4.344
Abnormal cell migration protein 10 - Caenorhabditis elegans			*2.391*				
Acidic mammalian chitinase precursor - Rattus norvegicus (Rat)	2.048		2.541				5.028
Aconitate hydratase, mitochondrial precursor - Bos taurus (Bovine)	3.77						
Aconitate hydratase, mitochondrial precursor - Saccharomyces cerevisiae (Baker_s yeast)	14.34	0.643	3.063	0.193	0.612		4.74
Actin, aortic smooth muscle - Rattus norvegicus (Rat)	2.911		3.661	0.523	0.527		4.311

Actin, cytoplasmic 1 - Mesocricetus auratus (Golden hamster)					0.602		
Actin-binding LIM protein 2 - Rattus norvegicus (Rat)	5.388		5.696	2.036	0.52	3.794	11.389
Actin-like protein 2 - Rattus norvegicus (Rat)	4.264				0.772		
Activating signal cointegrator 1 complex subunit 2 - Homo sapiens (Human)	2.09				0.636		
Activating signal cointegrator 1 complex subunit 3 - Homo sapiens (Human)	1.598	0.279	1.909	0.798	0.863	0.959	1.835
Activin receptor type 1B precursor - Rattus norvegicus (Rat)		0.366					
Acyl-coenzyme A oxidase 1, peroxisomal - Rattus norvegicus (Rat)					0.554		2.14
ADAM 17 precursor - Rattus norvegicus (Rat)	4.903				0.866		
ADAM 7 precursor - Rattus norvegicus (Rat)	5.099						
Adenomatous polyposis coli protein - Rattus norvegicus (Rat)	1.056	0.826		0.349			
Adenylate cyclase type 2 - Rattus norvegicus (Rat)	32.72				3.99		
Adenylate cyclase type 5 - Rattus norvegicus (Rat)		0.958	1.412				0.684
Adenylate cyclase type 6 - Rattus norvegicus (Rat)			1.358				

Adenylate cyclase type 8 - Rattus norvegicus (Rat)		0.526	6.244		0.194		
Adenylyl cyclase-associated protein 1 - Rattus norvegicus (Rat)					0.484		
AdoMet-dependent rRNA methyltransferase SPB1 - Candida glabrata (Yeast) (Torulopsis glabrata)			3.665	1.173			
Adrenodoxin, mitochondrial precursor - Rattus norvegicus (Rat)	10.8						
Advanced glycosylation end product-specific receptor precursor - Rattus norvegicus (Rat)		0.586					
Afamin precursor - Rattus norvegicus (Rat)	9.301	0.659	2.996	0.565	0.717	2.225	2.373
Aflatoxin B1 aldehyde reductase member 3 - Rattus norvegicus (Rat)	4.642		2.635	0.346	0.667		3.861
A-kinase anchor protein 11 - Rattus norvegicus (Rat)		1.115					
A-kinase anchor protein 5 - Rattus norvegicus (Rat)		0.496	5.162				4.461
A-kinase anchor protein 6 - Rattus norvegicus (Rat)	3.23	0.212	1.301				
Alanine--glyoxylate aminotransferase 2, mitochondrial precursor - Rattus norvegicus (Rat)	2.816		3.799		1.043		
Alcohol dehydrogenase 4 - Rattus norvegicus (Rat)					0.699		
Aldehyde dehydrogenase 1A3 -	4.649				0.522		

Rattus norvegicus (Rat)							
Aldehyde dehydrogenase 3B1 - Rattus norvegicus (Rat)	0.601	0.909	0.789		0.554		1.254
Aldehyde dehydrogenase, mitochondrial - Mesocricetus auratus (Golden hamster)							
Aldehyde oxidase - Rattus norvegicus (Rat)		0.591			0.585		
Aldo-keto reductase family 1 member C18 - Rattus norvegicus (Rat)					0.578		19.052
Aldose 1-epimerase - Rattus norvegicus (Rat)			2.503		0.636		
Allograft inflammatory factor 1 - Rattus norvegicus (Rat)	1.289		1.408		1.456		
All-trans-retinol 13,14-reductase precursor - Rattus norvegicus (Rat)			1.959	0.58	0.633	3.928	
Alpha-1-acid glycoprotein precursor - Rattus norvegicus (Rat)	2.331	18.187	2.376	1.241	0.685	6.401	2.542
Alpha-1-antiproteinase precursor - Rattus norvegicus (Rat)	7.309	1.105	3.941	2.098	0.624	9.013	6.033
Alpha-1-antitrypsin precursor - Mesocricetus auratus (Golden hamster)	3.47		5.508	1.44	0.606	6.63	7.027
Alpha-1-inhibitor 3 precursor - Rattus norvegicus (Rat)	3.003		2.532	1.033	0.57	1.026	2.866
Alpha-1-macroglobulin precursor - Rattus norvegicus (Rat)	2.017	0.515	3.041				5.14
Alpha-2-HS-glycoprotein precursor - Rattus norvegicus (Rat)	18.9	6.216	7.635	1.857	0.659	16.402	8.895

Alpha-2-macroglobulin precursor - Rattus norvegicus (Rat)			3.703		0.556		
Alpha-adducin - Rattus norvegicus (Rat)		1.214					
Alpha-enolase - Rattus norvegicus (Rat)	5.287		2.452	2.403	0.842		2.81
Alpha-S1-casein precursor - Rattus norvegicus (Rat)					0.585		
Alpha-soluble NSF attachment protein - Rattus norvegicus (Rat)							
AMBP protein precursor	3.5		2.546	1.206	1.198	3.389	1.997
Aminoacylase-1A - Rattus norvegicus (Rat)	7.067			2.892	0.808		1.756
Aminopeptidase N - Rattus norvegicus (Rat)	4.11	0.557	1.872	0.812	0.641		2.508
Androgen receptor - Rattus norvegicus (Rat)							
Androgen-induced proliferation inhibitor A - Xenopus laevis (African clawed frog)		2.894					
Angiopoietin-related protein 4 precursor - Rattus norvegicus (Rat)	0.839						
Angiotensinogen precursor - Rattus norvegicus (Rat)	4.871		3.036	1.512	1.026	4.426	3.332
ANK repeat and LEM domain-containing protein KIAA0692 homolog - Rattus norvegicus (Rat)					0.828		
Ankyrin repeat and BTB/POZ domain-containing protein 2 - Rattus norvegicus (Rat)			1.891		0.59		2.529

Ankyrin repeat and zinc finger domain-containing protein 1 - Rattus norvegicus (Rat)			2.164		0.501		2.492
AP-2 complex subunit mu-1 - Rattus norvegicus (Rat)							
Apolipoprotein A-I precursor - Rattus norvegicus (Rat)	4.227				0.479		2.68
Apolipoprotein A-II precursor - Rattus norvegicus (Rat)							
Apolipoprotein A-IV precursor - Rattus norvegicus (Rat)	4.535		3.954	0.722	0.599	5.214	4.129
Apolipoprotein B-100 precursor - Rattus norvegicus (Rat)			2.257		0.47		3.131
Apolipoprotein E precursor - Rattus norvegicus (Rat)					0.587		1.893
Apoptosis facilitator Bcl-2-like protein 14 - Rattus norvegicus (Rat)					1.026		
Apoptotic protease-activating factor 1 - Rattus norvegicus (Rat)			4.147		0.846		
Aprataxin - Mus musculus (Mouse)			3.056		0.463		
Aquaporin-1 - Rattus norvegicus (Rat)					0.672		
Arginine-glutamic acid dipeptide repeats protein - Rattus norvegicus (Rat)				0.621			1.858
Armadillo repeat-containing protein 5 - Rattus norvegicus (Rat)							
Artemis protein - Rattus							

norvegicus (Rat)							
Asparagine synthetase			8.076		0.514		10.219
Ataxin-10 - Rattus norvegicus (Rat)							
ATP synthase B chain, mitochondrial precursor - Rattus norvegicus (Rat)							
ATP synthase subunit 5, mitochondrial precursor - Candida glabrata (Yeast) (Torulopsis glabrata)			1.964				1.935
ATP synthase subunit beta, mitochondrial precursor - Rattus norvegicus (Rat)	9.419						
ATP-binding cassette sub-family A member 7 - Rattus norvegicus (Rat)			1.229		0.594		
ATP-binding cassette sub-family B member 7, mitochondrial precursor - Rattus norvegicus (Rat)	5.418						
ATP-binding cassette sub-family D member 3 - Rattus norvegicus (Rat)		2.395	3.499	0.344			5.069
ATP-binding cassette sub-family F member 1 - Rattus norvegicus (Rat)	0.434	5.352	0.747		0.746		0.872
ATP-binding cassette transporter CGR1 - Candida glabrata (Yeast) (Torulopsis glabrata)			2.693	8.439			

ATP-binding cassette transporter sub-family C member 8 - Rattus norvegicus (Rat)		0.436					2.459
ATP-citrate synthase - Bos taurus (Bovine)							
ATP-dependent RNA helicase DBP10 - Candida glabrata (Yeast) (Torulopsis glabrata)			3.484				
ATP-dependent RNA helicase DBP3 - Candida glabrata (Yeast) (Torulopsis glabrata)			3.858	1.904			
ATP-dependent RNA helicase DBP7 - Candida glabrata (Yeast) (Torulopsis glabrata)							6.389
ATP-dependent RNA helicase DDX25 - Rattus norvegicus (Rat)	0.835	0.899	1.281	0.285	0.524		5.024
ATP-dependent RNA helicase SUB2 - Candida glabrata (Yeast) (Torulopsis glabrata)			2.775				
ATP-dependent rRNA helicase RRP3 - Candida glabrata (Yeast) (Torulopsis glabrata)			2.594				3.058
ATP-sensitive inward rectifier potassium channel 12 - Rattus norvegicus (Rat)			6.1				10.078
Atrial natriuretic peptide receptor B precursor - Rattus norvegicus (Rat)	10.46						
AT-rich interactive domain-containing protein 4B - Rattus norvegicus (Rat)			5.65				

Attractin precursor - Rattus norvegicus (Rat)	5.109		5.106				
Autophagy-related protein 17 - Candida glabrata (Yeast) (Torulopsis glabrata)			5.808				7.534
Autophagy-related protein 2 - Candida glabrata (Yeast) (Torulopsis glabrata)			0.981	0.486			1.872
Autophagy-related protein 7 - Rattus norvegicus (Rat)		1.318					
Autophagy-related protein 9A - Rattus norvegicus (Rat)			5.344		0.614		
Axin-2 - Rattus norvegicus (Rat)			5.549				5.68
BAG family molecular chaperone regulator 5 - Rattus norvegicus (Rat)			2.725		0.645	9.869	
BarH-like 1 homeobox protein - Rattus norvegicus (Rat)				0.519			
Basic fibroblast growth factor receptor 1 precursor - Rattus norvegicus (Rat)		0.526		0.343			2.406
Beta-1,4-mannosyl-glycoprotein 4-beta-N-acetylglucosaminyltransferase - Rattus norvegicus (Rat)							2.625
Beta-2-glycoprotein 1 precursor - Rattus norvegicus (Rat)	3.392		3.264	0.644	0.634	3.892	4.259
Beta-2-microglobulin precursor - Rattus norvegicus (Rat)			1.829	2.43	0.977	2.22	
Beta-adducin - Rattus norvegicus		1.163					

(Rat)							
Beta-glucuronidase precursor - Rattus norvegicus (Rat)		2.834					0.45
Beta-microseminoprotein precursor - Rattus norvegicus (Rat)		0.766	3.696		0.511	1.533	5.3
Beta-type platelet-derived growth factor receptor precursor - Rattus norvegicus (Rat)		0.592					
Bifunctional UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase - Rattus norvegicus (Rat)	4.122						
Bile salt export pump - Rattus norvegicus (Rat)	3.53				0.863		
Bone morphogenetic protein receptor type IA precursor - Rattus norvegicus (Rat)	14.97				0.525		
Borealin - Rattus norvegicus (Rat)							
Brain-specific angiogenesis inhibitor 1-associated protein 2-like protein 1 - Rattus norvegicus (Rat)	1.979	0.84	0.885		4.022	2.186	1.109
Branched-chain-amino-acid aminotransferase, cytosolic - Rattus norvegicus (Rat)	0.928		1.44	0.392	0.555		3.008
Branchpoint-bridging protein - Candida glabrata (Yeast) (Torulopsis glabrata)			3.598				
Breast cancer type 2 susceptibility protein homolog - Rattus norvegicus (Rat)	2.519		3.72	7.413	0.994		2.297

Breast carcinoma amplified sequence 1 homolog - Rattus norvegicus (Rat)	1.114						
C-1-tetrahydrofolate synthase, cytoplasmic - Rattus norvegicus (Rat)			1.943				
Cadherin EGF LAG seven-pass G-type receptor 3 precursor - Rattus norvegicus (Rat)					1.066		
Cadherin-8 precursor - Rattus norvegicus (Rat)			1.476			1.458	2.06
Calbindin - Rattus norvegicus (Rat)	2.525	0.602	1.875				
Calcium/calmodulin-dependent protein kinase kinase 1 - Rattus norvegicus (Rat)	4.807		4.811			3.5	
Calcium/calmodulin-dependent protein kinase type II alpha chain - Rattus norvegicus (Rat)		1.299					
Calcium-dependent secretion activator 1 - Rattus norvegicus (Rat)	0.905	1.789	1.042	0.334	1.932	2.616	1.009
Calcyclin-binding protein - Rattus norvegicus (Rat)	1.312		1.704	0.393		1.201	1.924
Calicin - Rattus norvegicus (Rat)	40.06						
Calpain-3 - Rattus norvegicus (Rat)			2.112		2.243		
Calsyntenin-2 precursor - Rattus norvegicus (Rat)			2.574				
Canalicular multispecific organic			1.996		0.778		2.47

anion transporter 1 - Rattus norvegicus (Rat)							
CAP-Gly domain-containing linker protein 2 - Rattus norvegicus (Rat)				0.425			
CAP-Gly domain-containing linker protein 4 - Rattus norvegicus (Rat)			7.168				
Carbamoyl-phosphate synthase			2.01				
Carbohydrate sulfotransferase 10 - Mus musculus (Mouse)							
Carbohydrate sulfotransferase 11 - Danio rerio (Zebrafish) (Brachydanio rerio)			0.312	0.065			0.443
Carbohydrate sulfotransferase 13 - Homo sapiens (Human)					0.683		
Carbohydrate sulfotransferase D4ST1 - Danio rerio (Zebrafish) (Brachydanio rerio)			1.945				2.8
Carnitine O-acetyltransferase - Rattus norvegicus (Rat)					0.675		
Caspase-7 precursor - Mesocricetus auratus (Golden hamster)					1.501		
Catalase - Rattus norvegicus (Rat)	6.673		2.162	0.504	0.633		2.913
Catenin delta-2 - Rattus norvegicus (Rat)					1.012		1.11
Cathepsin S precursor - Rattus norvegicus (Rat)	2.656	0.381	1.59	0.495	0.76		1.955
CCAAT/enhancer-binding protein	4.974		3.708		0.638		6.532

delta - Rattus norvegicus (Rat)							
CD59 glycoprotein precursor - Rattus norvegicus (Rat)		0.518					
CDK5 and ABL1 enzyme substrate 1 - Homo sapiens (Human)		0.8	0.889		0.756		0.78
CDK5 regulatory subunit-associated protein 1 - Rattus norvegicus (Rat)	3.948		4.479	0.459	0.873	3.96	
Cell division protein kinase 5 - Rattus norvegicus (Rat)		0.422					
Centaurin-gamma 1 - Rattus norvegicus (Rat)		3.68					
Centromere protein U - Rattus norvegicus (Rat)	4.365		6.249	0.778	0.652		6.647
Ceramide glucosyltransferase - Rattus norvegicus (Rat)		0.478					
Ceruloplasmin precursor - Rattus norvegicus (Rat)	3.392		2.295	1.458	0.683	7.415	2.504
cGMP-dependent 3_,5_-cyclic phosphodiesterase - Rattus norvegicus (Rat)				0.635			
cGMP-dependent protein kinase 2 - Rattus norvegicus (Rat)	0.316	1.641					
cGMP-inhibited 3_,5_-cyclic phosphodiesterase B - Rattus norvegicus (Rat)	2.628						
Chitobiosyldiphosphodolichol beta-mannosyltransferase - Candida glabrata (Yeast)			0.585				0.987

(Torulopsis glabrata)							
Chloride channel protein 2 - Rattus norvegicus (Rat)	1.256		2.078		0.817		
Chloride channel protein ClC-Ka - Rattus norvegicus (Rat)		0.562					
Chordin precursor - Rattus norvegicus (Rat)			1.302				1.541
Chromodomain Y-like protein - Rattus norvegicus (Rat)			1.438		0.924	2.696	
Citrate synthase, mitochondrial precursor - Sus scrofa (Pig)	40.31	0.582	8.666	2.157	0.551	13.004	10.559
Class E vacuolar protein-sorting machinery protein HSE1 - Candida glabrata (Yeast) (Torulopsis glabrata)			26.429				17.192
Cleavage stimulation factor 50 kDa subunit - Rattus norvegicus (Rat)	0.458				1.229	0.516	
Clusterin precursor - Rattus norvegicus (Rat)	5.59		2.95		1.417		
Clusterin-like protein 1 precursor - Rattus norvegicus (Rat)			2.889				
Coatomer subunit beta - Rattus norvegicus (Rat)		0.938	2.181		0.758	1.467	4.904
Coiled-coil domain-containing protein 105 - Rattus norvegicus (Rat)							
Coiled-coil domain-containing protein 16 - Rattus norvegicus			2.094		1.065		1.874

(Rat)							
Coiled-coil domain-containing protein 41 - Rattus norvegicus (Rat)		3.107	1.645		0.665		2.253
Coiled-coil domain-containing protein 55 - Rattus norvegicus (Rat)					0.604		
Coiled-coil domain-containing protein 60 - Rattus norvegicus (Rat)			3.626	4.172	2.671		
Coiled-coil domain-containing protein 63 - Rattus norvegicus (Rat)					0.763		
Coiled-coil domain-containing protein 65 - Rattus norvegicus (Rat)							36.01
Coiled-coil domain-containing protein 93 - Rattus norvegicus (Rat)					0.469		3.021
Coiled-coil domain-containing protein 98 - Rattus norvegicus (Rat)		0.361					
Cold shock domain-containing protein E1 - Rattus norvegicus (Rat)			0.336		4.608	0.457	
Collagen alpha-1(I) chain precursor - Rattus norvegicus (Rat)							3.307
Complement C3 precursor	4.873		3.403	1.059	0.761	3.093	3.27
Complement C4 precursor	7.491	2.585	4.619	1.159	0.512		4.94

Complement component C6 precursor - Rattus norvegicus (Rat)	4.26						
Complement component C9 precursor - Rattus norvegicus (Rat)	6.067		2.786	1.023	0.805	5.086	3.768
Complement factor I precursor - Rattus norvegicus (Rat)	4.298		2.935		0.678		2.072
Connector enhancer of kinase suppressor of ras 2 - Rattus norvegicus (Rat)					0.715		
Contactin-1 precursor - Rattus norvegicus (Rat)	3.204						
Contactin-3 precursor - Rattus norvegicus (Rat)			3.829		0.706		
COP9 signalosome complex subunit 1 - Rattus norvegicus (Rat)			7.774				8.377
Copine-9 - Rattus norvegicus (Rat)			7.386				10.395
C-reactive protein precursor - Rattus norvegicus (Rat)	4.955		2.95	1.252	1.491	4.109	2.917
Crossover junction endonuclease MUS81 - Candida glabrata (Yeast) (Torulopsis glabrata)				0.422			2.593
C-type lectin domain family 11 member A precursor - Rattus norvegicus (Rat)		0.328					
Cullin-5 - Rattus norvegicus (Rat)		2.451					
Cullin-associated NEDD8-dissociated protein 2 - Rattus norvegicus (Rat)							
Cyclic AMP-dependent	0.445			0.673	1.077		

transcription factor ATF-2 - Rattus norvegicus (Rat)							
Cyclin-H - Rattus norvegicus (Rat)	5.18						
Cystathionine beta-synthase - Rattus norvegicus (Rat)			6.065		1.31		
Cystathionine gamma-lyase - Rattus norvegicus (Rat)	7.431		2.715	0.334	1.006		3.013
Cystatin-C precursor - Rattus norvegicus (Rat)	10.63		6.132	1.529	0.879	2.652	4.573
Cystatin-related protein 1 precursor - Rattus norvegicus (Rat)	1.058	1.339	3.188	0.814	0.681	0.966	1.001
Cystatin-related protein 2 precursor - Rattus norvegicus (Rat)		1.143	2.095		1.071		1.442
Cysteine sulfinic acid decarboxylase - Rattus norvegicus (Rat)		1.155					
Cysteine-rich with EGF-like domain protein 2 precursor - Rattus norvegicus (Rat)	5.948						
Cystic fibrosis transmembrane conductance regulator - Rattus norvegicus (Rat)		3.177	0.522		0.791		0.92
Cytochrome c, somatic - Rattus norvegicus (Rat)	0.471				0.539		2.658
Cytochrome P450 19 type 1 - Carassius auratus (Goldfish)			1.864		0.752		2.287
Cytochrome P450 1A1 - Mesocricetus auratus (Golden hamster)						1.027	
Cytochrome P450 27,	6.736						

mitochondrial precursor - Rattus norvegicus (Rat)							
Cytochrome P450 2A1 - Rattus norvegicus (Rat)	3.35		2.245	1.408	1.015		
Cytochrome P450 2C55 - Rattus norvegicus (Rat)			4.792				5.968
Cytochrome P450 2C6 - Rattus norvegicus (Rat)				1.664			
Cytochrome P450 2C70 - Rattus norvegicus (Rat)		3.674					
Cytochrome P450 3A1 - Rattus norvegicus (Rat)					1.018		
Cytochrome P450 3A10 - Mesocricetus auratus (Golden hamster)			8.301		0.568		6.283
Cytosolic acyl coenzyme A thioester hydrolase - Rattus norvegicus (Rat)		0.837					2.5
Cytosolic non-specific dipeptidase - Rattus norvegicus (Rat)	3.115		2.62		0.826		2.651
Cytosolic phospholipase A2 - Rattus norvegicus (Rat)		0.563					
Cytospin-A - Rattus norvegicus (Rat)			2.263	0.604	0.559	1.422	
Death-inducer obliterator 1 - Homo sapiens (Human)	3.185				1.439		
Deoxyribonuclease-1 precursor - Rattus norvegicus (Rat)	5.063	2.75	4.749			6.717	
Diacylglycerol kinase gamma - Rattus norvegicus (Rat)	2.568						

Dihydroorotate dehydrogenase, mitochondrial precursor - Rattus norvegicus (Rat)		0.266	5.979				
Dihydropyridine-sensitive L-type calcium channel subunits alpha-2/delta precursor			3.782	1.598			3.991
Dihydropyrimidinase - Rattus norvegicus (Rat)	6.264		2.649		0.623		3.843
Dihydropyrimidinase-related protein 5 - Rattus norvegicus (Rat)			3.182				4.348
Dihydroxyacetone phosphate acyltransferase - Rattus norvegicus (Rat)			2.835	2.484			2.607
Dihydroxy-acid dehydratase, mitochondrial precursor - Saccharomyces cerevisiae (Baker_s yeast)			2.259		0.697		1.185
Dimethylaniline monooxygenase		0.479	4.619	0.801			7.962
Dipeptidyl peptidase 4 - Rattus norvegicus (Rat)	8.887				0.534		
Disabled homolog 2-interacting protein - Rattus norvegicus (Rat)	3.769						
Disks large homolog 1 - Rattus norvegicus (Rat)			5.013				
Disks large homolog 2 - Rattus norvegicus (Rat)			0.98	1.323	0.994		1.47
Disks large homolog 3 - Rattus norvegicus (Rat)			2.492				3.97
Disks large-associated protein 3 - Rattus norvegicus (Rat)		0.478					

Disks large-associated protein 4 - Rattus norvegicus (Rat)		0.551		0.291			
DNA - Rattus norvegicus (Rat)		1.15					2.155
DNA ligase 1 - Rattus norvegicus (Rat)	0.791	3.181	0.46	0.242	0.777	0.242	
DNA polymerase alpha catalytic subunit - Rattus norvegicus (Rat)	7.042		2.613		1.322		
DNA polymerase epsilon subunit B - Candida glabrata (Yeast) (Torulopsis glabrata)							0.516
DNA polymerase epsilon, catalytic subunit A - Candida glabrata (Yeast) (Torulopsis glabrata)			0.869				0.808
DNA polymerase subunit delta 2 - Rattus norvegicus (Rat)		1.893					
DNA polymerase subunit gamma 1 - Rattus norvegicus (Rat)	2.802				0.748		
DNA repair protein RAD5 - Candida glabrata (Yeast) (Torulopsis glabrata)							2.18
DNA repair protein RAD50 - Rattus norvegicus (Rat)	10.58	0.543	8.336		0.356		14.341
DNA topoisomerase 1 - Rattus norvegicus (Rat)	11.84						
DNA topoisomerase 2 - Candida glabrata (Yeast) (Torulopsis glabrata)				6.875			
DNA topoisomerase 2-alpha - Rattus norvegicus (Rat)	7.902						
DNA-binding protein SMUBP-2 -	1.585		2.738	1.413	0.725	1.217	

Mesocricetus auratus (Golden hamster)							
DNA-directed RNA polymerase I subunit RPA1 - Rattus norvegicus (Rat)			2.516		0.697		1.821
DNA-directed RNA polymerase II subunit RPB2 - Candida glabrata (Yeast) (Torulopsis glabrata)			10.733	1.055			14.514
DnaJ homolog subfamily C member 16 precursor - Rattus norvegicus (Rat)			2.138	1.795	0.696		
DnaJ homolog subfamily C member 2 - Rattus norvegicus (Rat)	7.843		8.962		1.537		
DnaJ homolog subfamily C member 8 - Rattus norvegicus (Rat)							
DNA-repair protein XRCC1 - Rattus norvegicus (Rat)	2.892						
Double-stranded RNA-specific editase B2 - Rattus norvegicus (Rat)	1.249	1.963	0.393		0.586	0.993	
Dual oxidase 1 precursor - Rattus norvegicus (Rat)		0.743	2.518				2.666
Dual specificity mitogen-activated protein kinase kinase 7 - Rattus norvegicus (Rat)				0.948	0.594	4.968	
Dynactin subunit 1 - Rattus norvegicus (Rat)		2.374	5.013				5.894
Dynactin subunit 4 - Rattus norvegicus (Rat)			4.804				2.834

Dynamin-1 - Rattus norvegicus (Rat)					0.988		
Dynamin-like 120 kDa protein, mitochondrial precursor - Rattus norvegicus (Rat)					0.961		1.507
Dynein heavy chain, cytosolic - Rattus norvegicus (Rat)	5.388				0.67		
E2-induced gene 5 protein homolog - Rattus norvegicus (Rat)			2.581				
E3 ubiquitin-protein ligase BRE1B - Rattus norvegicus (Rat)	10.8						
E3 ubiquitin-protein ligase rififylin - Rattus norvegicus (Rat)	0.483	0.389	3.406		1.355		1.732
E3 ubiquitin-protein ligase RING1 - Rattus norvegicus (Rat)		6.109					
E3 ubiquitin-protein ligase RING2 - Rattus norvegicus (Rat)							
E3 ubiquitin-protein ligase RNF138 - Rattus norvegicus (Rat)		0.441	2.021	0.442	1.224		
Echinoderm microtubule-associated protein-like 5 - Rattus norvegicus (Rat)		0.424			4.26		14.217
Ecotropic viral integration site 5 protein homolog - Homo sapiens (Human)	5.063		2.414	0.78	0.598	2.883	
Ectonucleotide pyrophosphatase/phosphodiesterase family member 2 precursor - Rattus norvegicus (Rat)		0.511					
Elongation factor 1-alpha 1 -					0.337		

Rattus norvegicus (Rat)							
Elongation factor G - Apple proliferation phytoplasma			5.004				
Endothelin B receptor precursor - Rattus norvegicus (Rat)				0.575			
Endothelin-1 precursor - Rattus norvegicus (Rat)			3.072	1.663			
Endothelin-converting enzyme 1 - Rattus norvegicus (Rat)			1.163	0.879			
Enhancer of mRNA-decapping protein 4 - Rattus norvegicus (Rat)		0.451					
Ephrin type-A receptor 3 precursor - Rattus norvegicus (Rat)		0.483					
Ephrin type-A receptor 5 precursor - Rattus norvegicus (Rat)							
Epithelial-cadherin precursor - Rattus norvegicus (Rat)		0.792	3.343	1.923	0.843		2.182
Epoxide hydrolase 1 - Rattus norvegicus (Rat)	1.492		2.768	0.543	0.547	1.862	3.078
Equilibrative nucleoside transporter 2 - Homo sapiens (Human)							
ERGIC-53 protein precursor - Rattus norvegicus (Rat)		0.339	1.724				2.133
ESF1 homolog - Rattus norvegicus (Rat)	1.981		2.306	0.553	0.691		3.258
Estrogen receptor beta-2 - Carassius auratus (Goldfish)		0.609	2.377		1.288		3.863
Eukaryotic initiation factor 4A-II - Rattus norvegicus (Rat)			5.237		0.384		

Eukaryotic translation initiation factor 3 subunit 8 - Pongo pygmaeus (Orangutan)		0.5					
Excitatory amino acid transporter 1 - Rattus norvegicus (Rat)	1.648	0.804	3.929	0.789	0.681	1.457	7.427
Excitatory amino acid transporter 4 - Rattus norvegicus (Rat)	2.767						
Exocyst complex component 6 - Rattus norvegicus (Rat)					0.652		
Exocyst complex protein EXO70 - Candida glabrata (Yeast) (Torulopsis glabrata)			3.522				
Exportin-1 - Rattus norvegicus (Rat)					0.621		
Extracellular calcium-sensing receptor precursor - Rattus norvegicus (Rat)							5.711
Ezrin - Rattus norvegicus (Rat)	13.6		2.494		0.367		2.256
Fanconi anemia group C protein homolog - Rattus norvegicus (Rat)						3.335	
Fatty acid oxidation complex subunit alpha	3.596		3.989	1.998	0.762	3.165	3.709
Fatty acid synthase - Rattus norvegicus (Rat)							
Fetuin-B precursor - Rattus norvegicus (Rat)	5.378		3.687	2.054	0.811	5.021	3.958
Fibrinogen alpha chain precursor			1.554				
Fibrinogen beta chain precursor - Rattus norvegicus (Rat)			1.888		1.179		1.796
Fibrinogen gamma chain precursor			4.673		1.263		3.773

- Rattus norvegicus (Rat)							
Fibroblast growth factor 18 precursor - Rattus norvegicus (Rat)			3.102		0.546		4.024
Fibronectin precursor - Rattus norvegicus (Rat)	3.957	0.722			0.605		2.083
Filamin-A-interacting protein 1 - Rattus norvegicus (Rat)	6.926	1.255	1.296		0.598		1.757
Filensin - Rattus norvegicus (Rat)			1.19	1.807	1.26		0.66
FKBP12-rapamycin complex-associated protein - Rattus norvegicus (Rat)	2.468		3.038		0.688	5.288	3.39
Focal adhesion kinase 1 - Rattus norvegicus (Rat)					0.476		
Folliculin - Rattus norvegicus (Rat)			2.604				3.465
Fos-related antigen 2 - Rattus norvegicus (Rat)			2.257				3.077
Four and a half LIM domains protein 1 - Rattus norvegicus (Rat)	3.717		1.94		0.549	6.776	
Four and a half LIM domains protein 5 - Rattus norvegicus (Rat)					1.139		
Fragile X mental retardation syndrome-related protein 1 - Rattus norvegicus (Rat)			2.934				
Fructose-1,6-bisphosphatase 1 - Rattus norvegicus (Rat)	6.116		6.693	0.579	1.374		6.084
Fructose-bisphosphate aldolase B - Rattus norvegicus (Rat)	1.546		2.708	0.329	0.515		3.79
Fumarylacetoacetase - Rattus norvegicus (Rat)	4.692		0.743	0.678	1.394		1.674

G patch domain-containing protein 4 - Rattus norvegicus (Rat)	25.96				2.501		8.425
G protein-activated inward rectifier potassium channel 2 - Mesocricetus auratus (Golden hamster)							
G protein-coupled receptor kinase 5 - Rattus norvegicus (Rat)			2.015				
G2/mitotic-specific cyclin-B2 - Mesocricetus auratus (Golden hamster)			2.575		0.714		4.465
Gamma-adducin - Rattus norvegicus (Rat)		0.883					2.12
Gamma-aminobutyric-acid receptor subunit rho-1 precursor - Rattus norvegicus (Rat)							
Gamma-glutamyl hydrolase precursor - Rattus norvegicus (Rat)	6.939						
Gamma-glutamyltranspeptidase 1 precursor - Rattus norvegicus (Rat)			3.657		0.699		
Gap junction beta-1 protein - Rattus norvegicus (Rat)			2.007	4.98	1.679	5.325	
Gelsolin precursor - Rattus norvegicus (Rat)	3.371	0.535	2.756	0.724	1.044	4.927	2.578
Glandular kallikrein-10 precursor - Rattus norvegicus (Rat)		4.074					
Glandular kallikrein-12, submandibular/renal precursor - Rattus norvegicus (Rat)	6.038		1.804	0.64	0.446		
Gliomedin - Rattus norvegicus	0.386						

(Rat)							
Glucagon-like peptide 2 receptor precursor - Rattus norvegicus (Rat)			0.688		1.559		0.751
Glucocorticoid receptor DNA-binding factor 1 - Rattus norvegicus (Rat)			6.111		0.436		
Glucokinase regulatory protein - Rattus norvegicus (Rat)		0.62	2.256				
Glucosamine--fructose-6-phosphate aminotransferase		0.65			0.743		
Glucose-6-phosphate 1-dehydrogenase - Ceratitis capitata (Mediterranean fruit fly)	9.943		2.063	2.284	0.527		
Glutamate dehydrogenase 1, mitochondrial precursor - Rattus norvegicus (Rat)	4.218		5.961		0.586		
Glutamate receptor 4 precursor - Rattus norvegicus (Rat)	7.882						
Glutamate receptor, ionotropic kainate 2 precursor - Rattus norvegicus (Rat)		2.748					
Glutamate--cysteine ligase catalytic subunit - Rattus norvegicus (Rat)	5.327		2.893	0.582	0.702		3.296
Glutamate--cysteine ligase regulatory subunit - Rattus norvegicus (Rat)	4.086		2.918	0.321	0.363		4.192
Glutamyl aminopeptidase - Rattus norvegicus (Rat)			2.063				1.702
Glutathione peroxidase 3 precursor					0.602		2.147

- Rattus norvegicus (Rat)							
Glutathione S-transferase alpha-1 - Rattus norvegicus (Rat)	4.484		3.03	0.378	0.516		4.79
Glutathione S-transferase P - Cricetulus migratorius (Armenian hamster)	2.026		1.964		0.633		2.475
Glutathione synthetase - Rattus norvegicus (Rat)			2.247		0.514		2.414
Glycerol-3-phosphate dehydrogenase	3.641		2.734				
Glycerol-3-phosphate dehydrogenase, mitochondrial precursor - Rattus norvegicus (Rat)	5.546						
Glycine dehydrogenase	2.49		2.278		0.615		
Glycine receptor subunit alpha-1 precursor - Rattus norvegicus (Rat)							
Glycylpeptide N-tetradecanoyltransferase - Candida glabrata (Yeast) (Torulopsis glabrata)			1.641				
Glypican-1 precursor - Rattus norvegicus (Rat)					0.742		
Golgi apparatus protein 1 homolog precursor - Caenorhabditis elegans				0.496	0.613		
Golgi apparatus protein 1 precursor - Gallus gallus (Chicken)	5.497		3.844		0.511	4.312	2.672
Golgi apparatus protein 1 precursor - Homo sapiens (Human)		0.587					

Golgin subfamily A member 2 - Rattus norvegicus (Rat)	0.311					0.759	
GON-4-like protein - Rattus norvegicus (Rat)	1.626	1.01	0.905		1.767	1.875	0.812
GPI inositol-deacylase - Candida glabrata (Yeast) (Torulopsis glabrata)			5.265				
G-protein coupled receptor family C group 6 member A precursor - Rattus norvegicus (Rat)			2.209		0.657		
GRAM domain-containing protein 1A - Rattus norvegicus (Rat)	5.931				0.609		
Granulins precursor							
Gremlin-1 precursor - Rattus norvegicus (Rat)		11.699		0.384			0.26
Growth hormone receptor precursor - Rattus norvegicus (Rat)	8.03				1.328		13.626
Guanine deaminase - Rattus norvegicus (Rat)	6.31	1.092	5.213		0.85	10.53	8.416
Guanine nucleotide exchange factor LTE1 - Candida glabrata (Yeast) (Torulopsis glabrata)				0.916			
Guanylate cyclase soluble subunit beta-2 - Rattus norvegicus (Rat)					1.344		
H-2 class II histocompatibility antigen gamma chain - Rattus norvegicus (Rat)							
Hamartin - Rattus norvegicus (Rat)	5.226		2.189		0.558		2.787
Haptoglobin precursor	3.663		6.323	1.585	0.847	7.281	7.442
Haptoglobin precursor - Rattus	5.122	1.528	4.975	2.813	1.166	10.97	4.648

norvegicus (Rat)						3	
Heat shock 70 kDa protein 1L - Rattus norvegicus (Rat)			7.199	0.503	0.301		8.151
Heat shock 70 kDa protein 4 - Rattus norvegicus (Rat)	1.529						
Heat shock cognate 71 kDa protein - Rattus norvegicus (Rat)					0.765		2.437
Heat shock protein 105 kDa - Rattus norvegicus (Rat)					0.696		
Heat shock protein 75 kDa, mitochondrial precursor - Rattus norvegicus (Rat)			8.657		1.745		16.27
Heat shock protein HSP 90-beta - Rattus norvegicus (Rat)	4.404						
Helicase SWR1 - Candida glabrata (Yeast) (Torulopsis glabrata)			2.868				
Hemoglobin subunit alpha-1/2 - Rattus norvegicus (Rat)	1.77	0.911				0.438	
Hemoglobin subunit beta-1 - Rattus norvegicus (Rat)	2.14	0.424				0.626	
Hemoglobin subunit beta-2 - Rattus norvegicus (Rat)						0.212	
Hemopexin precursor - Rattus norvegicus (Rat)	6.041	0.925	5.847	2.992	0.944	9.239	7.22
Hepatocyte growth factor precursor - Rattus norvegicus (Rat)	6.262		3.299	3.966	0.786		4.648
Hepatoma-derived growth factor-related protein 3 - Rattus norvegicus (Rat)				1.798			

Hereditary hemochromatosis protein homolog precursor - Ceratotherium simum (White rhinoceros) (Square-lipped rhinoceros)			0.551				0.699
Heterogeneous nuclear ribonucleoprotein K - Rattus norvegicus (Rat)							1.011
Heterogeneous nuclear ribonucleoprotein M - Rattus norvegicus (Rat)	2.845		5.248	2.353	1.254		6.655
Hexokinase-1 - Rattus norvegicus (Rat)					0.688		
Hexokinase-3 - Rattus norvegicus (Rat)			3.546		1.173		3.875
Histidine decarboxylase - Rattus norvegicus (Rat)		0.53					
Histone acetyltransferase MYST2 - Rattus norvegicus (Rat)					0.598		
Histone H2A type 1-C - Rattus norvegicus (Rat)	6.13		6.829	0.398	1.101		4.573
Histone H2B type 1 - Rattus norvegicus (Rat)			3.594		0.87		
Histone-lysine N-methyltransferase SETMAR - Rattus norvegicus (Rat)			1.997				
Histone-lysine N-methyltransferase SUV420H1 - Rattus norvegicus (Rat)				0.525	0.604		
Homeobox protein Nkx-2.2 - Mesocricetus auratus (Golden	4.043						

hamster)							
Homeodomain-interacting protein kinase 4 - Rattus norvegicus (Rat)	3.654		5.695				
Homer protein homolog 3 - Rattus norvegicus (Rat)	2.905						
Host cell factor - Mesocricetus auratus (Golden hamster)	7.764		3.912	5.142	1.293	1.563	4.082
Host cell factor 2 - Rattus norvegicus (Rat)					1.046		
HSPB1-associated protein 1 - Rattus norvegicus (Rat)				0.442			
Huntingtin - Rattus norvegicus (Rat)	11.59	0.405	3.352		0.738		2.345
Hydroxyacid oxidase 2 - Rattus norvegicus (Rat)	5.297		3.553	0.466	0.848		4.458
Hydroxyacylglutathione hydrolase - Rattus norvegicus (Rat)					0.697		
Ig gamma-1 chain C region - Rattus norvegicus (Rat)	4.324				0.736		2.016
Ig gamma-2A chain C region - Rattus norvegicus (Rat)	2.632		2.093	0.519	0.621	1.955	3.801
Ig gamma-2B chain C region - Rattus norvegicus (Rat)							
Ig kappa chain C region, A allele - Rattus norvegicus (Rat)	2.235	1.168	2.008	2.922	1.17	4.475	1.851
Ig lambda-2 chain C region - Rattus norvegicus (Rat)	12.26	1.273	3.798		0.566	2.507	5.192
Immunoglobulin superfamily member 10 precursor - Rattus norvegicus (Rat)	10.03	1.209	2.588	0.54	0.62		3.41

Import inner membrane translocase subunit TIM44, mitochondrial precursor - Rattus norvegicus (Rat)		0.354					
Inactive dipeptidyl peptidase 10 - Rattus norvegicus (Rat)			4.914				
Inactive ubiquitin carboxyl-terminal hydrolase 54 - Rattus norvegicus (Rat)			1.477		0.635		1.951
Inhibitor of nuclear factor kappa-B kinase subunit beta - Rattus norvegicus (Rat)							
Inositol 1,4,5-trisphosphate receptor type 1 - Rattus norvegicus (Rat)			5.078	0.255			
Inositol 1,4,5-trisphosphate receptor type 3 - Rattus norvegicus (Rat)	2.074	0.358	2.345	0.448	0.508		3.323
Inositol-trisphosphate 3-kinase A - Rattus norvegicus (Rat)	3.326			4.549			
Insulin receptor substrate 1 - Mus musculus (Mouse)	4.462		3.601		0.701		
Insulin receptor substrate 2 - Homo sapiens (Human)							
Insulin-like growth factor 1 receptor precursor - Rattus norvegicus (Rat)	1.991		2.74		0.664		2.243
Insulin-like growth factor 2 mRNA-binding protein 1 - Rattus norvegicus (Rat)			5.465		0.645		

Insulin-like growth factor-binding protein 3 precursor - Rattus norvegicus (Rat)	22.72		6.112		0.574		
Insulin-like growth factor-binding protein 5 precursor - Rattus norvegicus (Rat)							
Integrator complex subunit 1 - Homo sapiens (Human)			3.646				5.427
Integrator complex subunit 10 - Gallus gallus (Chicken)	2.292			1.011			
Integrator complex subunit 11 - Homo sapiens (Human)							
Integrator complex subunit 4 - Homo sapiens (Human)					0.595		
Integrin alpha-1 precursor - Rattus norvegicus (Rat)	0.284						
Integrin beta-6 precursor - Rattus norvegicus (Rat)			1.056		0.712		1.095
Inter-alpha-trypsin inhibitor heavy chain H3 precursor - Mesocricetus auratus (Golden hamster)			5.571	0.557	0.484		
Interferon regulatory factor 1 - Rattus norvegicus (Rat)		0.535					
Interferon-induced GTP-binding protein Mx1 - Rattus norvegicus (Rat)	5.107				1.151		
Interferon-induced guanylate-binding protein 2 - Rattus norvegicus (Rat)	0.9		0.839				

Interferon-induced protein with tetratricopeptide repeats 2 - Mus musculus (Mouse)	11.35						
Interferon-related developmental regulator 1 - Rattus norvegicus (Rat)	3.687	0.961			1.48		1.525
Interleukin-1 receptor accessory protein precursor - Rattus norvegicus (Rat)							
Interleukin-1 receptor-associated kinase-like 2 - Rattus norvegicus (Rat)			6.773		0.733		7.967
Interleukin-10 precursor - Rattus norvegicus (Rat)			1.928				
Interleukin-6 receptor subunit beta precursor - Rattus norvegicus (Rat)			11.318			4.887	13.536
Intraflagellar transport 81 - Rattus norvegicus (Rat)			2.04		0.539		2.739
IQ and ubiquitin-like domain-containing protein - Rattus norvegicus (Rat)		1.209			1.363		0.73
IQ domain-containing protein D - Rattus norvegicus (Rat)	5.491		4.859				
Iron-responsive element-binding protein 1 - Rattus norvegicus (Rat)			1.8		0.914		3.174
Iron-sulfur clusters transporter ATM1, mitochondrial precursor - Candida glabrata (Yeast) (Torulopsis glabrata)			3.465	2.724			3.67
Isocitrate dehydrogenase	3.764	0.285	3.5	0.476	0.67		9.837

Isocitrate lyase - Candida glabrata (Yeast) (Torulopsis glabrata)			2.904				4.612
Jagged-1 precursor - Rattus norvegicus (Rat)	3.967	2.583					
JmjC domain-containing histone demethylation protein 2A - Rattus norvegicus (Rat)							1.893
Kalirin - Rattus norvegicus (Rat)	3.772		2.982	0.355	0.461	2.799	
Katanin p60 ATPase-containing subunit A1 - Rattus norvegicus (Rat)	3.27					3.747	
Kelch domain-containing protein 3 - Rattus norvegicus (Rat)					0.69		
Kelch repeat and BTB domain-containing protein 10 - Rattus norvegicus (Rat)			4.385		0.427		6.229
Keratin type II cuticular Hb2 - Mus musculus (Mouse)							
Keratin, type I cuticular Ha6 - Homo sapiens (Human)							
Keratin, type I cytoskeletal 10 - Homo sapiens (Human)							
Keratin, type I cytoskeletal 17 - Homo sapiens (Human)			2.566				
Keratin, type I cytoskeletal 47 kDa - Xenopus laevis (African clawed frog)		1.011					
Keratin, type I cytoskeletal 9 - Homo sapiens (Human)	3.557					10.775	
Keratin, type II cytoskeletal 1b -		0.687	0.588		0.692		

Homo sapiens (Human)							
Keratin-associated protein 4-8 - Homo sapiens (Human)	9.196		2.521				3.251
Keratin-associated protein 5-3 - Homo sapiens (Human)	2.732				0.802		
Keratin-associated protein 5-4 - Homo sapiens (Human)					1.098		
Keratinocyte proline-rich protein - Rattus norvegicus (Rat)		1.619					
Ketohexokinase - Rattus norvegicus (Rat)	9.621				0.991		3.177
KHG/KDPG aldolase		1.536					
Kinesin heavy chain - Rattus norvegicus (Rat)					0.69		
Kinesin-like protein KIF1B - Rattus norvegicus (Rat)	5.143				0.618		3.183
Kininogen-1 precursor	2.365		2.429		0.597		
Kynurenine/alpha-aminoadipate aminotransferase mitochondrial precursor - Rattus norvegicus (Rat)	4.869		3.443	0.442	0.654		5.027
Kynurenine--oxoglutarate transaminase 3 - Danio rerio (Zebrafish) (Brachydanio rerio)			4.11				
L-2-hydroxyglutarate dehydrogenase, mitochondrial precursor - Homo sapiens (Human)			1.12				1.337
L-2-hydroxyglutarate dehydrogenase, mitochondrial precursor - Mus musculus (Mouse)			1.645		0.986		

Lactase-phlorizin hydrolase precursor - Rattus norvegicus (Rat)	6.639		4.085				
Lambda-crystallin homolog - Rattus norvegicus (Rat)			2.333		0.497	6.693	
Laminin subunit beta-2 precursor - Rattus norvegicus (Rat)			2.639		0.664		
La-related protein 7 - Rattus norvegicus (Rat)							
Large neutral amino acids transporter small subunit 2 - Rattus norvegicus (Rat)		0.586					
Large proline-rich protein BAT2 - Rattus norvegicus (Rat)	26.39		18.134		3.918	40.727	
Latent-transforming growth factor beta-binding protein 1 precursor - Rattus norvegicus (Rat)			3.207				3.699
Latent-transforming growth factor beta-binding protein 2 precursor - Rattus norvegicus (Rat)							
Lethal(2) giant larvae protein homolog 1 - Rattus norvegicus (Rat)			1.288				
Leucine zipper protein 1 - Rattus norvegicus (Rat)			2.25	1.225	1.095		
Leucine zipper putative tumor suppressor 1 - Rattus norvegicus (Rat)		1.81	2.769		0.278	4.061	4.817
Leucine-rich repeat flightless-interacting protein 1 - Rattus norvegicus (Rat)	3.323				0.566	4.099	

Leucine-rich repeat neuronal protein 3 precursor - Rattus norvegicus (Rat)			0.828		0.694		
Leucine-rich repeat-containing protein 41 - Rattus norvegicus (Rat)					0.987		5.286
Leucine-rich repeat-containing protein 48 - Rattus norvegicus (Rat)							
Leucine-rich repeat-containing protein 59 - Rattus norvegicus (Rat)		0.867					
Leucine-rich repeat-containing protein 8A - Rattus norvegicus (Rat)					1.054		
Leucine-rich repeat-containing protein 8D - Rattus norvegicus (Rat)					1.411		
Leukemia inhibitory factor receptor precursor - Rattus norvegicus (Rat)			1.763		0.756		
Leukocyte common antigen precursor - Rattus norvegicus (Rat)					0.761		
Light-sensor Protein kinase			5.121		0.559		
LIM and SH3 domain protein 1 - Rattus norvegicus (Rat)			3		0.636		3.19
LIM domain kinase 2 - Rattus norvegicus (Rat)	3.874						
LIM homeobox transcription factor 1 alpha - Mesocricetus auratus (Golden hamster)		0.596					

Limkain-b1 - Rattus norvegicus (Rat)	0.64						
Liprin-alpha-3 - Rattus norvegicus (Rat)		1.374					1.947
Liprin-alpha-4 - Rattus norvegicus (Rat)		2.701		1.052		1.816	
LisH domain-containing protein ARMC9 - Rattus norvegicus (Rat)	3.843						
Liver carboxylesterase 1 precursor - Rattus norvegicus (Rat)	8.993		2.192		0.654		2.753
Liver carboxylesterase 4 precursor - Rattus norvegicus (Rat)	7.623	0.616	9.727	1.851	0.641	9.369	10.35
L-lactate dehydrogenase C chain - Rattus norvegicus (Rat)							2.548
Long-chain-fatty-acid--CoA ligase 1 - Rattus norvegicus (Rat)					1.004		
Long-chain-fatty-acid--CoA ligase 5 - Rattus norvegicus (Rat)	7.775		5.668	0.485	0.326	10.35	
Low-density lipoprotein receptor-related protein 2 precursor - Rattus norvegicus (Rat)		0.398	1.803	0.594	0.707		2.568
Lupus La protein homolog - Rattus norvegicus (Rat)		0.868					
Lysozyme C type 1 precursor - Rattus norvegicus (Rat)	4.082		2.787		0.807		2.219
Macrophage metalloelastase precursor - Rattus norvegicus (Rat)		0.627					
Major urinary protein - Rattus rattus (Black rat)	7.377	5.67		0.403	3.839		
Major urinary protein precursor -	2.794	3.187	1.728	1.223	1.262	3.196	1.276

Rattus norvegicus (Rat)							
Malate dehydrogenase, cytoplasmic - Rattus norvegicus (Rat)			1.95	0.446	0.57		2.788
Mannan endo-1,6-alpha-mannosidase DCW1 precursor - Candida glabrata (Yeast) (Torulopsis glabrata)				2.564			
Mannan-binding lectin serine protease 2 precursor - Rattus norvegicus (Rat)	3.309		2.074		0.759		
Mannose-6-phosphate isomerase - Rattus norvegicus (Rat)			0.854		1.324		1.083
MAP kinase-activated protein kinase 3 - Rattus norvegicus (Rat)		1.283					2.078
Mast cell protease 1 precursor - Rattus norvegicus (Rat)				0.159			
Meckelin - Rattus norvegicus (Rat)			4.093				
Mediator of DNA damage checkpoint protein 1 - Rattus norvegicus (Rat)			3.905	1.23	0.755		
Meiotic sister-chromatid recombination protein 3 - Candida glabrata (Yeast) (Torulopsis glabrata)			1.93				
Melanocortin receptor 5 - Rattus norvegicus (Rat)		2.485	4.12				3.647
Meprin A subunit alpha precursor - Rattus norvegicus (Rat)		1.306					

Metabotropic glutamate receptor 4 precursor - Rattus norvegicus (Rat)					0.925		1.374
Metabotropic glutamate receptor 5 precursor - Rattus norvegicus (Rat)	1.136		1.404		0.571		1.784
Metallothionein-2 - Mesocricetus auratus (Golden hamster)	18.64		3.956				4.78
Metallothionein-3 - Rattus norvegicus (Rat)			2.958			3.372	
Methionine aminopeptidase 2 - Rattus norvegicus (Rat)	2.295						
Methyl-CpG-binding protein 2 - Rattus norvegicus (Rat)					0.511		
Microtubule-associated protein 1A - Rattus norvegicus (Rat)	2.58						
Microtubule-associated protein 1B - Rattus norvegicus (Rat)							
Microtubule-associated protein 2 - Rattus norvegicus (Rat)	8.29		6.515		0.625		
Midline-1 - Rattus norvegicus (Rat)					0.518		
MIT domain-containing protein 1 - Rattus norvegicus (Rat)			4.809				
Mitochondrial ATPase complex subunit ATP10 - Candida glabrata (Yeast) (Torulopsis glabrata)				0.653			
Mitochondrial intermediate peptidase, mitochondrial precursor - Rattus norvegicus (Rat)					0.434		
Mitofusin-1 - Rattus norvegicus (Rat)					0.68		

Mitogen-activated protein kinase kinase kinase 1 - Rattus norvegicus (Rat)			5.983				7.671
Mitogen-activated protein kinase kinase kinase kinase 3 - Rattus norvegicus (Rat)	2.032				0.71		
Moesin - Rattus norvegicus (Rat)	2.964				0.457		1.396
Mucin-2 precursor - Rattus norvegicus (Rat)	0.979	0.392			0.762		
Mu-crystallin homolog - Rattus norvegicus (Rat)		2.554			0.419		
Multidrug resistance-associated protein 1 - Rattus norvegicus (Rat)					0.925		
Multidrug resistance-associated protein 5 - Rattus norvegicus (Rat)	6.668			0.825	0.369		5.617
Multiple epidermal growth factor-like domains 6 precursor - Rattus norvegicus (Rat)					0.684		
Multiple epidermal growth factor-like domains 8 - Rattus norvegicus (Rat)		0.489					
Multiple PDZ domain protein - Rattus norvegicus (Rat)							
Murinoglobulin-1 precursor - Rattus norvegicus (Rat)	5.339				0.555		
Muscarinic acetylcholine receptor M5 - Rattus norvegicus (Rat)							2.16
Muscle, skeletal receptor tyrosine protein kinase precursor - Rattus norvegicus (Rat)					0.605		

Myelin transcription factor 1-like protein - Rattus norvegicus (Rat)			2.168		0.675		3.057
Myosin light chain kinase 2, skeletal/cardiac muscle - Rattus norvegicus (Rat)			9.705				17.682
Myosin light polypeptide 6 - Rattus norvegicus (Rat)	10.07						
Myosin regulatory light chain 2, skeletal muscle isoform - Rattus norvegicus (Rat)							
Myosin-10 - Rattus norvegicus (Rat)	7.825		5.771	0.382	0.968	4.699	
Myosin-3 - Rattus norvegicus (Rat)	2.172	4.594	1.727	0.357	0.769		2.037
Myosin-4 - Rattus norvegicus (Rat)			2.076			0.355	2.419
Myosin-6 - Mesocricetus auratus (Golden hamster)							
Myosin-7 - Mesocricetus auratus (Golden hamster)	1.435						
Myosin-9 - Rattus norvegicus (Rat)	6.338	0.514	3.332	1.727	1.336	7.57	2.623
Myosin-Ib - Rattus norvegicus (Rat)	3.984	5.868	2.923	0.94	0.581		3.761
Myosin-Id - Rattus norvegicus (Rat)			1.836				
Myosin-IXb - Rattus norvegicus (Rat)			2.754		0.444		4.027
Myosin-Va - Rattus norvegicus (Rat)	5.577				1.297		

N-acetylgalactosamine 4-sulfate 6-O-sulfotransferase - Rattus norvegicus (Rat)							
N-acetylgalactosaminyltransferase 7 - Rattus norvegicus (Rat)	1.485		0.754	0.608			0.712
N-acylneuraminate cytidylyltransferase - Rattus norvegicus (Rat)				1.765			1.706
NAD-dependent deacetylase sirtuin-2 - Rattus norvegicus (Rat)			2.47		0.619		3.186
NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial precursor - Rattus norvegicus (Rat)							2.244
Nck-associated protein 1 - Rattus norvegicus (Rat)		2.735					
Nerve growth factor gamma chain precursor - Rattus norvegicus (Rat)	5.313	1.412	2.422			1.012	1.451
Nestin - Rattus norvegicus (Rat)	3.919						
Netrin receptor UNC5C precursor - Rattus norvegicus (Rat)							
Neurexin-1-alpha precursor - Rattus norvegicus (Rat)	9.312						
Neurexin-3-alpha precursor - Rattus norvegicus (Rat)			1.988	0.251	0.429		3.836
Neurexophilin-3 precursor - Rattus norvegicus (Rat)					0.797		
Neurofascin precursor - Rattus norvegicus (Rat)			3.792				5.434
Neurofibromin - Rattus norvegicus (Rat)			1.974		0.69	6.327	2.148

Neurofilament heavy polypeptide - Rattus norvegicus (Rat)	4.726			1.385	0.732		
Neurogenic locus notch homolog protein 2 precursor - Rattus norvegicus (Rat)	2.598	1.114	4.784		0.8		5.19
Neurogenic locus notch homolog protein 3 precursor - Rattus norvegicus (Rat)		6.465					
Neurolysin, mitochondrial precursor - Rattus norvegicus (Rat)					0.785		4.544
Neuronal acetylcholine receptor subunit alpha-2 precursor - Rattus norvegicus (Rat)					1.09		
Neuronal acetylcholine receptor subunit alpha-3 precursor - Rattus norvegicus (Rat)		0.343					
Neuronal pentraxin-1 precursor - Rattus norvegicus (Rat)	6.824				1.323		7.93
Neuropeptide Y receptor type 1 - Rattus norvegicus (Rat)					0.496		
Neuropilin-1 precursor - Rattus norvegicus (Rat)			1.982	0.862	0.501	2.17	1.941
Neurotensin receptor type 1 - Rattus norvegicus (Rat)				0.333			
Neutral and basic amino acid transport protein rBAT - Rattus norvegicus (Rat)					0.494		1.562
Neutral ceramidase - Rattus norvegicus (Rat)			5.407		0.648	6.375	
Neutrophil antibiotic peptide NP-4					1.063		

precursor - Rattus norvegicus (Rat)							
Nicalin precursor - Rattus norvegicus (Rat)					0.749		
Nitrate reductase	4.631	0.588	4.617	5.136	0.866	4.433	3.633
Nitrilase homolog 1 - Rattus norvegicus (Rat)	3.974						
Noelin-3 precursor - Rattus norvegicus (Rat)			2.164				
Non-muscle caldesmon - Rattus norvegicus (Rat)	8.121		2.514		2.149		1.735
NT-3 growth factor receptor precursor - Rattus norvegicus (Rat)	3.758		6.783				
Nuclear migration protein NUM1 - Saccharomyces cerevisiae (Baker_s yeast)	5.136	0.359	2.853	0.48	0.642	6.12	3.692
Nuclear migration protein unc-83 - Caenorhabditis elegans			3.357	1.065	0.681		3.233
Nuclear mitotic apparatus protein 1 - Homo sapiens (Human)	1.275	1.119	1.954		2.188		1.363
Nuclear pore complex protein Nup107 - Rattus norvegicus (Rat)			1.944	0.457			
Nuclear pore complex protein Nup153 - Rattus norvegicus (Rat)	3.931		2.651	1.003	0.55		3.613
Nuclear protein localization protein 4 homolog - Rattus norvegicus (Rat)							
Nuclear receptor coactivator 2 - Rattus norvegicus (Rat)							
Nuclear receptor coactivator 3 - Rattus norvegicus (Rat)	6.218		1.524		1.061		

Nuclear receptor ROR-beta - Rattus norvegicus (Rat)	14.86						0.567
Nucleobindin-1 precursor - Rattus norvegicus (Rat)	5.361						
Nucleolar GTP-binding protein 1 - Rattus norvegicus (Rat)					0.529		
Nucleolar GTP-binding protein 2 - Candida glabrata (Yeast) (Torulopsis glabrata)							10.115
Nucleolar protein 12 - Candida glabrata (Yeast) (Torulopsis glabrata)				0.909			
Nucleolin - Mesocricetus auratus (Golden hamster)							
Odorant-binding protein precursor - Rattus norvegicus (Rat)					0.543		2.105
Oleandomycin polyketide synthase, modules 5 and 6 - Streptomyces antibioticus	4.636		4.598	1.19	0.379	8.098	7.634
Oligoribonuclease, mitochondrial precursor - Rattus norvegicus (Rat)			2.07		0.474		2.258
Optineurin - Rattus norvegicus (Rat)					0.604		
Organic cation transporter 3 - Rattus norvegicus (Rat)					0.629		
Ornithine aminotransferase, mitochondrial precursor - Rattus norvegicus (Rat)		1.29					
Orphan nuclear receptor NR1D2 - Rattus norvegicus (Rat)			5.44				

Orphan sodium- and chloride-dependent neurotransmitter transporter NTT4 - Rattus norvegicus (Rat)		0.555	3.068		1.016		
Osteopontin precursor - Rattus norvegicus (Rat)					0.799		
Oxidation resistance protein 1 - Rattus norvegicus (Rat)		0.494					
p130Cas-associated protein - Rattus norvegicus (Rat)							
PAB-dependent poly(A)-specific ribonuclease subunit 2 - Rattus norvegicus (Rat)		0.416					
Paired box protein Pax-8 - Rattus norvegicus (Rat)		1.851					
Pancreatic alpha-amylase precursor - Rattus norvegicus (Rat)		1.232					
Partitioning-defective 3 homolog - Rattus norvegicus (Rat)					0.634		
Parvalbumin alpha - Rattus norvegicus (Rat)	4.329						
Patatin-like phospholipase domain-containing protein 2 - Rattus norvegicus (Rat)		0.66					
Patatin-like phospholipase domain-containing protein 7 - Rattus norvegicus (Rat)						11.827	
PDZ domain-containing protein 1 - Rattus norvegicus (Rat)	4.025						
PDZ domain-containing protein 2 -		0.528			0.681	0.332	2.478

Rattus norvegicus (Rat)							
PDZ domain-containing RING finger protein 3 - Rattus norvegicus (Rat)					0.725		
Peptide methionine sulfoxide reductase - Rattus norvegicus (Rat)			2.099				
Peptide-N(4)-(N-acetyl-beta-glucosaminyl)asparagine amidase - Rattus norvegicus (Rat)	1.265		1.583			0.965	
Peptidyl-prolyl cis-trans isomerase G - Rattus norvegicus (Rat)	7.058		7.792		0.544		
Periaxin - Rattus norvegicus (Rat)	3.375	1.849	4.321		0.728		4.03
Period circadian protein homolog 2 - Rattus norvegicus (Rat)					1.76		
Period circadian protein homolog 3 - Rattus norvegicus (Rat)					1.233		4.67
Peripherin-2 - Rattus norvegicus (Rat)		1.997					
Peroxiredoxin-1 - Rattus norvegicus (Rat)	4.785		3.356	0.362	0.523		2.959
Peroxiredoxin-6 - Rattus norvegicus (Rat)			3.625		0.678		2.195
Peroxisomal biogenesis factor 3 - Rattus norvegicus (Rat)					1.025		
Peroxisomal Lon protease homolog 2 - Rattus norvegicus (Rat)	2.493	0.644	2.631		0.514		3.815
Peroxisome proliferator-activated receptor delta - Mus musculus (Mouse)	5.87		3.912				4

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha - Mus musculus (Mouse)	2.714		3.003	0.541	0.531		
Peroxisome proliferator-activated receptor gamma coactivator 1-alpha - Sus scrofa (Pig)	5.43				1.331		
Peroxisome proliferator-activated receptor gamma coactivator 1-beta - Mus musculus (Mouse)					0.991		
Peroxisome proliferator-activated receptor gamma coactivator 1-beta - Rattus norvegicus (Rat)					0.757		
Peroxisome proliferator-activated receptor-binding protein - Homo sapiens (Human)							2.588
PEX5-related protein - Rattus norvegicus (Rat)		0.748	1.226				
PH domain leucine-rich repeat protein phosphatase - Rattus norvegicus (Rat)			2.262				
Phosphatidylethanolamine-binding protein 1 - Rattus norvegicus (Rat)		0.303	3.805				3.814
Phosphatidylinositol 4,5-bisphosphate 5-phosphatase A - Rattus norvegicus (Rat)							
Phosphatidylinositol 4-kinase type 2-alpha - Rattus norvegicus (Rat)	2.633						
Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta isoform - Rattus norvegicus (Rat)		0.648					

Phosphatidylinositol-4-phosphate 3-kinase C2 domain-containing gamma polypeptide - Rattus norvegicus (Rat)		0.464					
Phosphoenolpyruvate carboxykinase	9.421	10.388					
Phosphoglycerate kinase 2 - Equus caballus (Horse)			2.403				2.471
Phosphoglycerate mutase 1 - Bos taurus (Bovine)	2.489						
Phosphoglycerate mutase family member 5 precursor - Xenopus tropicalis (Western clawed frog) (Silurana tropicalis)			3.496				
Phosphoinositide 3-kinase regulatory subunit 4 - Rattus norvegicus (Rat)			1.55				
Phospholipase A2 precursor - Rattus norvegicus (Rat)	4.772						
Phospholipase D1 - Rattus norvegicus (Rat)	2.211		4.542		0.326		5.453
pH-response regulator protein palF/RIM8 - Candida glabrata (Yeast) (Torulopsis glabrata)							4.671
Plasma kallikrein precursor - Rattus norvegicus (Rat)			4.192				
Plasma membrane calcium-transporting ATPase 2 - Rattus norvegicus (Rat)		0.382					
Plasma protease C1 inhibitor precursor - Rattus norvegicus (Rat)							

Plasma retinol-binding protein precursor - Rattus norvegicus (Rat)			1.974	0.593	0.764	3.527	2.384
Plasminogen precursor - Rattus norvegicus (Rat)	4.029	5.293	2.162	0.72	0.954	4.051	2.418
Pleckstrin - Rattus norvegicus (Rat)			2.172				
Pleckstrin homology domain-containing family F member 1 - Rattus norvegicus (Rat)			2.986				4.693
Pleckstrin homology-like domain family B member 1 - Rattus norvegicus (Rat)	9.153	1.75	12.073	2.149	2.679		14.369
Plectin-1 - Rattus norvegicus (Rat)	3.128	0.393	5.425	2.942	1.212		4.974
Podoplanin precursor - Rattus norvegicus (Rat)				1.039			
Polyadenylate-binding protein 1 - Rattus norvegicus (Rat)		0.879	2.849				3.072
Potassium channel subfamily T member 1 - Rattus norvegicus (Rat)	2.633		3.196				5.956
Potassium voltage-gated channel subfamily H member 1 - Rattus norvegicus (Rat)					0.705	1.513	
Potassium voltage-gated channel subfamily H member 5 - Rattus norvegicus (Rat)		1.694	1.877		0.567		2.038
Potassium voltage-gated channel subfamily H member 7 - Rattus norvegicus (Rat)		0.258					
Potassium-transporting ATPase					1.032	2.614	

alpha chain 2 - Rattus norvegicus (Rat)							
Pre-mRNA-splicing factor RSE1 - Candida glabrata (Yeast) (Torulopsis glabrata)							1.805
Pre-mRNA-splicing factor SLU7 - Rattus norvegicus (Rat)	4.331						
Probable ATP-dependent RNA helicase DDX46 - Rattus norvegicus (Rat)	1.532	0.449	0.842	0.391	0.592		1.777
Probable ATP-dependent RNA helicase DDX59 - Rattus norvegicus (Rat)					0.657		
Probable butyrate kinase 1 - Thermotoga maritima		4.063					
Probable Coiled-coil domain-containing protein 8 - Rattus norvegicus (Rat)							0.43
Probable DNA dC->dU-editing enzyme APOBEC3 - Rattus norvegicus (Rat)					0.422		9.44
Probable E3 ubiquitin-protein ligase RNF190 - Rattus norvegicus (Rat)		0.542	1.766	0.773	0.647		
Probable G-protein coupled receptor 119 - Rattus norvegicus (Rat)	4.86			0.591	1.125		
Probable kinetochore protein NDC80 - Candida glabrata (Yeast) (Torulopsis glabrata)			2.52				3.196

Probable metalloprotease ARX1 - Candida glabrata (Yeast) (Torulopsis glabrata)							1.277
Probable proteasome maturation factor ump1 - Schizosaccharomyces pombe (Fission yeast)							2.304
Probable U3 small nucleolar RNA-associated protein 11 - Rattus norvegicus (Rat)			2.057				
Probasin precursor - Rattus norvegicus (Rat)	1.514	3.34	3.611	0.632	0.908	2.53	3.696
Procollagen C-endopeptidase enhancer 1 precursor - Rattus norvegicus (Rat)			2.893				3.907
Procollagen-lysine,2-oxoglutarate 5-dioxygenase precursor - Caenorhabditis elegans	7.792						
Pro-epidermal growth factor precursor - Rattus norvegicus (Rat)	4.68	1.771	5.759	5.622	0.617	11.639	2.538
Profilin-1 - Rattus norvegicus (Rat)	1.635						
Prolactin-inducible protein homolog precursor - Rattus norvegicus (Rat)		0.544					
Proliferating cell nuclear antigen - Drosophila melanogaster (Fruit fly)							
Proliferating cell nuclear antigen - Xenopus laevis (African clawed frog)							3.131

Proline-, glutamic acid- and leucine-rich protein 1 - Rattus norvegicus (Rat)			0.671				
Pro-neuregulin-1, membrane-bound isoform precursor - Rattus norvegicus (Rat)			1.74				
Propionyl-CoA carboxylase alpha chain, mitochondrial precursor - Rattus norvegicus (Rat)				0.513			
Propionyl-CoA carboxylase beta chain, mitochondrial precursor - Rattus norvegicus (Rat)					0.608		
Proprotein convertase subtilisin/kexin type 7 precursor - Rattus norvegicus (Rat)					0.964		
Prostaglandin-H2 D-isomerase precursor - Rattus norvegicus (Rat)	0.481	0.366	2.752		0.932		2.005
Prostatic spermine-binding protein precursor - Rattus norvegicus (Rat)		0.511					
Prostatic steroid-binding protein C1 precursor - Rattus norvegicus (Rat)	0.498	1.113	0.949	0.433	0.789	4.28	0.874
Prostatic steroid-binding protein C2 precursor - Rattus norvegicus (Rat)	2.332	1.15	1.053	1.805	1.041	1.466	0.455
Protein ARMCX6 - Rattus norvegicus (Rat)			1.954	0.521	1.471		
Protein bassoon - Rattus norvegicus (Rat)	1.013		2.95		0.691		2.276
Protein BUD31 homolog - Rattus norvegicus (Rat)	6.816		16.018	1.773			4.982

Protein citXG			1.487				
Protein Dom3Z - Rattus norvegicus (Rat)		0.617					
Protein FAM101B - Rattus norvegicus (Rat)		0.499					
Protein FAM69B - Rattus norvegicus (Rat)	3.604				0.68		
Protein KIAA0082 homolog - Rattus norvegicus (Rat)			3.087				3.394
Protein kinase C alpha type - Rattus norvegicus (Rat)	6.35		2.123	0.531			
Protein kinase C delta type - Rattus norvegicus (Rat)			2.823		0.741		5.439
Protein kinase C eta type - Rattus norvegicus (Rat)					1.44		
Protein kinase C-binding protein NELL1 precursor - Rattus norvegicus (Rat)					0.652		
Protein NOV homolog precursor - Rattus norvegicus (Rat)			2.722		0.314		
Protein O-linked-mannose beta-1,2-N-acetylglucosaminyltransferase 1 - Rattus norvegicus (Rat)							
Protein OSCP1 - Rattus norvegicus (Rat)	1.484		1.478	0.851			
Protein piccolo - Rattus norvegicus (Rat)	2.386	0.847	3.697		0.579	2.829	2.39
Protein RAI1 - Candida glabrata (Yeast) (Torulopsis glabrata)			1.008	0.396			

Protein retinal degeneration B - Drosophila melanogaster (Fruit fly)							
Protein SDA1 homolog - Rattus norvegicus (Rat)		0.684	1.053				1.284
Protein Shroom2 - Rattus norvegicus (Rat)			1.236				
Protein ZNF365 - Rattus norvegicus (Rat)			5.277				9.726
Protein ZNF403 - Rattus norvegicus (Rat)			2.886		0.665		
Prothrombin precursor - Rattus norvegicus (Rat)	3.705		2.638	1.149	0.663	1.977	2.241
Protocadherin Fat 2 precursor - Rattus norvegicus (Rat)	4.726	1.116					
Proton-coupled amino acid transporter 1 - Rattus norvegicus (Rat)			2.614		0.5		3.583
Proto-oncogene tyrosine-protein kinase FER - Rattus norvegicus (Rat)			2.345				4.611
Proto-oncogene vav - Rattus norvegicus (Rat)		0.438					
Pseudouridylate synthase PUS5 - Candida glabrata (Yeast) (Torulopsis glabrata)			5.229	4.501			3.094
Puratrophin-1 - Homo sapiens (Human)					0.802		
Putative ATP-dependent RNA helicase DHX30 - Rattus				9.456	0.568		

norvegicus (Rat)							
Putative dihydroxy-acid dehydratase, mitochondrial precursor - Schizosaccharomyces pombe (Fission yeast)					1.442	5.495	
Putative RNA exonuclease NEF-sp - Rattus norvegicus (Rat)							
Putative rRNA methyltransferase 3 - Rattus norvegicus (Rat)						0.337	
Putative uncharacterized protein ENST00000281581 homolog - Rattus norvegicus (Rat)			10.3	0.602	0.302	12.159	17.412
Pyridoxine-5_-phosphate oxidase - Rattus norvegicus (Rat)					0.504		
Pyruvate dehydrogenase E1 component alpha subunit, somatic form, mitochondrial precursor - Rattus norvegicus (Rat)	4.755	0.465	2.684	0.66	1.206	0.661	
Pyruvate kinase isozymes M1/M2 - Rattus norvegicus (Rat)	3.195		3.369		0.818		3.713
Quinone oxidoreductase - Rattus norvegicus (Rat)	3.97		4.107		0.614		4.065
Rab effector MyRIP - Rattus norvegicus (Rat)		0.53					
Rab GTPase-binding effector protein 1 - Rattus norvegicus (Rat)		0.568					
RAB3A-interacting protein - Rattus norvegicus (Rat)					0.514		
RAC-alpha serine/threonine-protein kinase - Rattus norvegicus							

(Rat)							
RAC-gamma serine/threonine-protein kinase - Rattus norvegicus (Rat)					0.904		
RalA-binding protein 1 - Rattus norvegicus (Rat)	4.298		4.659	1.661	0.918		
Rap guanine nucleotide exchange factor 3 - Rattus norvegicus (Rat)							
Ras-related protein Rab-13 - Mesocricetus auratus (Golden hamster)			2.346				
Ras-related protein Rab-4A - Rattus norvegicus (Rat)					0.752		
Ras-related protein Rap-1b precursor - Rattus norvegicus (Rat)			1.673		1.508		2.168
Receptor-interacting serine/threonine-protein kinase 5 - Rattus norvegicus (Rat)	2.933						
Regenerating islet-derived protein 3 gamma precursor - Rattus norvegicus (Rat)		0.907	2.999	0.433	0.764		2.53
Regenerating islet-derived protein 4 precursor - Homo sapiens (Human)	3.744		2.138	2.321	1.498	2.843	
Regulating synaptic membrane exocytosis protein 1 - Rattus norvegicus (Rat)	1.11						
Regulating synaptic membrane exocytosis protein 2 - Rattus norvegicus (Rat)					1.591		

Regulator of G-protein signaling 3 - Rattus norvegicus (Rat)		6.398					12.796
Reticulon-3 - Rattus norvegicus (Rat)	3.725		3.633				3.391
Retinoblastoma-associated protein - Rattus norvegicus (Rat)		1.281	2.529				
Rho GTPase-activating protein 20 - Rattus norvegicus (Rat)			3.918				
Rho GTPase-activating protein 7 - Rattus norvegicus (Rat)					0.837		
Rho guanine nucleotide exchange factor 1 - Rattus norvegicus (Rat)		1.731					
Rho-associated protein kinase 1 - Rattus norvegicus (Rat)					0.657		
Rho-associated protein kinase 2 - Rattus norvegicus (Rat)	1.762	1.172	0.992		0.641		1.455
Ribonuclease 4 precursor - Rattus norvegicus (Rat)	4.502		2.975		1.193		
Ribonuclease H2 subunit B - Rattus norvegicus (Rat)				0.178			
Ribonuclease UK114 - Rattus norvegicus (Rat)			2.571		0.625		3.565
RING finger protein 39 - Rattus norvegicus (Rat)	2.783		2.164		0.697		
RWD domain-containing protein 4 - Rattus norvegicus (Rat)		0.398					
SAPK substrate protein 1 - Danio rerio (Zebrafish) (Brachydanio rerio)			1.233				1.712
Sarcolemmal membrane-		0.486	3.003		0.613	1.646	4.905

associated protein - Rattus norvegicus (Rat)							
Sarcosine dehydrogenase, mitochondrial precursor - Rattus norvegicus (Rat)							
Scaffold attachment factor B - Rattus norvegicus (Rat)			3.232		1.328		3.89
SCO-spondin precursor - Rattus norvegicus (Rat)	4.981		2.214		0.636		
Sec1 family domain-containing protein 1 - Rattus norvegicus (Rat)			3.786	0.665	0.491		
SEC14-like protein 2 - Rattus norvegicus (Rat)			3.275		0.649		4.577
Secretin receptor precursor - Rattus norvegicus (Rat)	1.686						
Secretoglobin family 2A member 2 precursor - Rattus norvegicus (Rat)	5.04	1.054	4.755	1.505	0.595		6.688
Selenium-binding protein 1 - Rattus norvegicus (Rat)	11.67						
Selenoprotein P precursor - Rattus norvegicus (Rat)	6.023				0.584		
Seminal vesicle protein 2 precursor - Rattus norvegicus (Rat)		0.9	1.267		1.392		
Seminal vesicle secretory protein 2 precursor - Rattus norvegicus (Rat)		0.423	0.59	0.617		0.266	0.399
Sentrin-specific protease 2 - Rattus norvegicus (Rat)	4.465						
Septin-7 - Rattus norvegicus (Rat)	11.27		6.049	5.47	0.982	4.891	10.664

Septin-9 - Rattus norvegicus (Rat)	3.744		5.328	3.222	1.823		
Serine protease inhibitor A3K precursor - Rattus norvegicus (Rat)	4.724	1.147	2.751	0.831	0.665	3.595	3.233
Serine protease inhibitor A3L precursor - Rattus norvegicus (Rat)	5.119	1.386	2.92	0.625	0.753	2.697	3.2
Serine protease inhibitor A3N precursor - Rattus norvegicus (Rat)	6.341		4.122	1.884	0.877	5.528	4.42
Serine protease inhibitor Kazal-type 3 precursor - Rattus norvegicus (Rat)			2.462		0.698		3.61
Serine/threonine-protein kinase MARK2 - Rattus norvegicus (Rat)		0.607		0.511			50.761
Serine/threonine-protein kinase MEC1 - Candida glabrata (Yeast) (Torulopsis glabrata)							2.249
Serine/threonine-protein kinase MRCK alpha - Rattus norvegicus (Rat)			1.216				
Serine/threonine-protein kinase N2 - Rattus norvegicus (Rat)			4.05	0.486	0.794		4.242
Serine/threonine-protein kinase Nek6 - Rattus norvegicus (Rat)	3.668						
Serine/threonine-protein kinase PAK 2 - Rattus norvegicus (Rat)			1.904	0.621	0.736		
Serine/threonine-protein kinase PCTAIRE-1 - Rattus norvegicus (Rat)	2.941		3.897		0.886	5.633	
Serine/threonine-protein kinase PLK1 - Rattus norvegicus (Rat)			3.097				
Serine/threonine-protein kinase	3.978	1.686					

PLK2 - Rattus norvegicus (Rat)							
Serine/threonine-protein kinase SNF1-like kinase 1 - Rattus norvegicus (Rat)			1.809	0.841	0.62	5.242	
Serine/threonine-protein kinase STE20 - Candida glabrata (Yeast) (Torulopsis glabrata)			0.654	0.511			0.965
Serine/threonine-protein kinase WNK1 - Rattus norvegicus (Rat)							
Serine/threonine-protein phosphatase 1 regulatory subunit 10 - Rattus norvegicus (Rat)		1.36					
Serine--pyruvate aminotransferase, mitochondrial precursor - Rattus norvegicus (Rat)					0.661		
Serotransferrin precursor - Rattus norvegicus (Rat)	8.746	1.318	6.429	2.25	0.777	14.451	9.47
Serpin H1 precursor - Rattus norvegicus (Rat)					0.641		
Serum albumin precursor - Rattus norvegicus (Rat)	11.27	1.594	11.739	4.421	1.539	20.378	15.357
SH2 domain-containing protein 4A - Rattus norvegicus (Rat)							
SH3 and multiple ankyrin repeat domains protein 2 - Rattus norvegicus (Rat)	0.479				0.452		
SH3 and multiple ankyrin repeat domains protein 3 - Rattus norvegicus (Rat)					0.732		

SH3 domain and tetratricopeptide repeats-containing protein 1 - Homo sapiens (Human)		0.551		0.374	0.646		2.152
SH3 domain-containing kinase-binding protein 1 - Rattus norvegicus (Rat)		8.289					
SH3-containing GRB2-like protein 3 - Rattus norvegicus (Rat)					0.541		
Signal transducer and activator of transcription 3 - Rattus norvegicus (Rat)	2.906						3.05
Signal-induced proliferation-associated 1-like protein 1 - Homo sapiens (Human)			1.675		1.217		2.11
Signal-induced proliferation-associated 1-like protein 1 - Mus musculus (Mouse)	3.254						
Slit homolog 1 protein precursor - Rattus norvegicus (Rat)	1.389						
Slit homolog 2 protein precursor - Rattus norvegicus (Rat)	3.241		2.914			1.622	
Slit homolog 3 protein precursor - Rattus norvegicus (Rat)			4.618	2.034	0.762		3.829
Small inducible cytokine B5 precursor - Rattus norvegicus (Rat)	5.859		2.767				
SNF-related serine/threonine-protein kinase - Rattus norvegicus (Rat)					1.187		
Sodium bicarbonate cotransporter 3 - Rattus norvegicus (Rat)		0.411					

Sodium channel protein type 10 subunit alpha - Rattus norvegicus (Rat)	6.232						2.594
Sodium channel protein type 2 subunit alpha - Rattus norvegicus (Rat)			2.072				
Sodium channel protein type 3 subunit alpha - Rattus norvegicus (Rat)			2.154		0.915		2.743
Sodium channel protein type 4 subunit alpha - Rattus norvegicus (Rat)		1.599					
Sodium/potassium-transporting ATPase subunit alpha-1 precursor - Rattus norvegicus (Rat)	6.184				1.164		
Sodium/potassium-transporting ATPase subunit alpha-2 precursor - Rattus norvegicus (Rat)		0.444					
Solute carrier family 12 member 1 - Rattus norvegicus (Rat)			2.219				
Solute carrier family 12 member 4 - Rattus norvegicus (Rat)		0.839					
Solute carrier family 2, facilitated glucose transporter member 8 - Rattus norvegicus (Rat)				0.822			
Solute carrier organic anion transporter family member 1A5 - Rattus norvegicus (Rat)							
Solute carrier organic anion transporter family member 1B2 - Rattus norvegicus (Rat)	0.542	0.283			0.576		

Solute carrier organic anion transporter family member 1C1 - Rattus norvegicus (Rat)	0.52						
Sorbitol dehydrogenase - Rattus norvegicus (Rat)	5.541		1.069				1.131
Sorting nexin-1 - Rattus norvegicus (Rat)		0.586					
Sorting nexin-4 - Candida glabrata (Yeast) (Torulopsis glabrata)			2.52				3.339
Spectrin alpha chain, brain - Rattus norvegicus (Rat)	7.381		6.316	2.389	0.639		10.577
Spectrin beta chain, brain 2 - Rattus norvegicus (Rat)	2.308	1.13	2.408		0.721	1.36	
Spermatogenic leucine zipper protein 1 - Rattus norvegicus (Rat)							
Sphingomyelin phosphodiesterase 3 - Rattus norvegicus (Rat)					0.586		3.168
Sphingosine-1-phosphate lyase 1 - Rattus norvegicus (Rat)							
Spindle apparatus protein lin-5 - Caenorhabditis elegans	5.099				0.366		
Spleen protein 1 precursor - Rattus norvegicus (Rat)	4.435		2.615	2.216	0.97		2.579
Spliceosome RNA helicase Bat1 - Rattus norvegicus (Rat)							2.189
Splicing factor 4 - Rattus norvegicus (Rat)			2.265				1.364
Splicing factor, arginine/serine-rich 2 - Rattus norvegicus (Rat)							2.027

Spore wall maturation protein DIT1 - Saccharomyces cerevisiae (Baker_s yeast)			2.429				
Stabilin-2 precursor - Rattus norvegicus (Rat)	7.852		6.48	1.174	0.564		7.109
STE20-like serine/threonine-protein kinase - Rattus norvegicus (Rat)							
Steroidogenic factor 1 - Rattus norvegicus (Rat)	11.42		8.062				8.053
Striated muscle-specific serine/threonine protein kinase - Rattus norvegicus (Rat)				0.396			
Stromal interaction molecule 1 precursor - Rattus norvegicus (Rat)	5.64						
Stromelysin-2 precursor - Rattus norvegicus (Rat)		0.681		0.773			
Structural maintenance of chromosomes protein 1A - Rattus norvegicus (Rat)	14.75	1.644	16.094	1.874	1.054		
Structural maintenance of chromosomes protein 3 - Rattus norvegicus (Rat)					1.135		
Submandibular glandular kallikrein-9 precursor - Rattus norvegicus (Rat)	3.311	1.549					0.58
Succinate dehydrogenase							3.242
Succinyl-CoA ligase				0.349	0.458		
Sulfite reductase	6.935				0.983		
Sulfotransferase 1C2 - Rattus	8.187				1.818		

norvegicus (Rat)							
Sulfotransferase 1C2A - Rattus norvegicus (Rat)					1.053		
Superoxide dismutase		0.975	2.692	0.586	0.405		3.192
Sushi repeat-containing protein SRPX precursor - Rattus norvegicus (Rat)			2.837				3.54
SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily D member 2 - Rattus norvegicus (Rat)	2.118						
Synaptojanin-1 - Rattus norvegicus (Rat)	2.52		3.575	0.596	0.518		
Synaptonemal complex protein 1 - Mesocricetus auratus (Golden hamster)							
Synaptonemal complex protein 2 - Rattus norvegicus (Rat)	1.763		2.977				
Synaptotagmin-like protein 5 - Rattus norvegicus (Rat)			3.557		0.733		
Synembryn-A - Rattus norvegicus (Rat)				0.596	0.474		
Syntaxin-18 - Rattus norvegicus (Rat)			2.42	0.478			3.765
Syntaxin-binding protein 2 - Rattus norvegicus (Rat)							
T-cell surface glycoprotein CD4 precursor - Rattus norvegicus (Rat)					0.374		7.218

T-complex protein 1 subunit alpha - Rattus norvegicus (Rat)			1.691		0.807		2.096
Tektin-4 - Rattus norvegicus (Rat)		0.424					
Telomerase protein component 1 - Rattus norvegicus (Rat)	4.613		3.499				4.746
Testin - Rattus norvegicus (Rat)	3.911		2.064				
Tetratricopeptide repeat protein 1 - Mus musculus (Mouse)	4.021						
Tetratricopeptide repeat protein 12 - Homo sapiens (Human)	2.298		2.121	0.841	0.553		
Tetratricopeptide repeat protein 12 - Mus musculus (Mouse)		0.525					
Tetratricopeptide repeat protein 14 - Homo sapiens (Human)				0.233	0.551		
Tetratricopeptide repeat protein 18 - Homo sapiens (Human)	7.654						
Tetratricopeptide repeat protein 21 homolog - Caenorhabditis briggsae					0.543		3.004
Tetratricopeptide repeat protein 21B - Homo sapiens (Human)	2.814	0.619	1.902				
Tetratricopeptide repeat protein 21B - Xenopus laevis (African clawed frog)					0.622		
Tetratricopeptide repeat protein 23 - Mus musculus (Mouse)							3.085
Tetratricopeptide repeat protein 25 - Xenopus laevis (African clawed frog)	2.204		2.697		0.541		3.53
Tetratricopeptide repeat protein 26 - Homo sapiens (Human)					0.515		

Tetratricopeptide repeat protein 3 - Homo sapiens (Human)	3.705	0.666	3.945		0.601		6.985
Tetratricopeptide repeat protein 31 - Homo sapiens (Human)		0.28					
Tetratricopeptide repeat protein 37 - Xenopus laevis (African clawed frog)	0.647	3.579		0.633			0.561
Tetratricopeptide repeat protein 7A - Homo sapiens (Human)			9.168				
Tetratricopeptide repeat protein 7B - Homo sapiens (Human)			1.056				1.155
TGF-beta-inducible nuclear protein 1 - Rattus norvegicus (Rat)	0.413				0.6		
THAP domain-containing protein 1 - Rattus norvegicus (Rat)	5.523						
Thioredoxin domain-containing protein 2 - Rattus norvegicus (Rat)				0.858			
Thyroglobulin precursor - Rattus norvegicus (Rat)			6.143				10.155
Thyroid hormone receptor-associated protein 3 - Rattus norvegicus (Rat)			1.9	2.6	0.677	0.4	2.66
Tissue factor pathway inhibitor precursor - Rattus norvegicus (Rat)				0.268			
T-kininogen 1 precursor - Rattus norvegicus (Rat)	4.523	3.161	4.096	2.837	0.926	5.625	4.715
T-kininogen 2 precursor - Rattus norvegicus (Rat)	3.175		2.904	3.16	1.459	7.707	3.182
Tonin precursor - Rattus norvegicus (Rat)		6.853					

TPR repeat-containing protein C12orf30 homolog - Rattus norvegicus (Rat)			0.431	0.571	1.443		
Transaldolase - Rattus norvegicus (Rat)	4.277						3.163
Transcription elongation factor A protein 1 - Rattus norvegicus (Rat)			2.228				
Transcription elongation factor B polypeptide 3 - Rattus norvegicus (Rat)							5.191
Transcription elongation factor SPT6 - Candida glabrata (Yeast) (Torulopsis glabrata)			2.489				
Transcription factor IWS1 - Candida glabrata (Yeast) (Torulopsis glabrata)				1.759			
Transcription initiation factor IIA gamma chain - Rattus norvegicus (Rat)					1.035		
Transcription initiation factor TFIID subunit 1 - Mesocricetus auratus (Golden hamster)					0.541		
Transcription termination factor, mitochondrial precursor - Rattus norvegicus (Rat)		1.32	2.282				
Transcriptional adapter 2-like - Rattus norvegicus (Rat)		0.312		1.585			
Transferrin receptor protein 1 - Rattus norvegicus (Rat)					0.983		

Transient receptor potential cation channel subfamily M member 4 - Rattus norvegicus (Rat)			2.085		0.788		
Transient receptor potential cation channel subfamily V member 5 - Rattus norvegicus (Rat)			1.358	1.172		0.361	1.445
Transient receptor potential cation channel subfamily V member 6 - Rattus norvegicus (Rat)				0.491		0.743	
Translation initiation factor eIF-2B subunit delta - Rattus norvegicus (Rat)	18.64		10.491	11.662	1.598	29.427	8.971
Transmembrane 9 superfamily protein member 2 precursor - Rattus norvegicus (Rat)	3.331		3.112				
Transmembrane protein 55B - Rattus norvegicus (Rat)		0.465		1.693	0.793		
TraT complement resistance protein precursor - Escherichia coli							
Trefoil factor 3 precursor - Rattus norvegicus (Rat)		0.95					
Trifunctional enzyme subunit alpha, mitochondrial precursor - Rattus norvegicus (Rat)							
Triosephosphate isomerase - Rattus norvegicus (Rat)					0.95		2.331
Tripartite motif-containing protein 17 - Rattus norvegicus (Rat)		1.973			0.673		
Tripartite motif-containing protein 39 - Rattus norvegicus (Rat)							3.904

Tripartite motif-containing protein 69 - Rattus norvegicus (Rat)			5.293		1.299		
tRNA pseudouridine synthase B - Mycobacterium paratuberculosis					2.04		
Tropomodulin-2 - Rattus norvegicus (Rat)	4.918	2.083			1.067	1.335	
Troponin T, fast skeletal muscle - Rattus norvegicus (Rat)			2.083				
Tubulin-specific chaperone E - Rattus norvegicus (Rat)					0.787		
Tubulointerstitial nephritis antigen-like precursor - Rattus norvegicus (Rat)					0.653		
Tudor domain-containing protein 7 - Rattus norvegicus (Rat)							3.548
Tumor necrosis factor receptor superfamily member 1B precursor - Rattus norvegicus (Rat)			2.305		0.315		
Tumor protein p73-like - Rattus norvegicus (Rat)		1.359					
Type II inositol-3,4-bisphosphate 4-phosphatase - Rattus norvegicus (Rat)							
Tyrosine-protein kinase JAK2 - Rattus norvegicus (Rat)			2.862	5.361	0.76		
U4/U6.U5 tri-snRNP-associated protein 1 - Rattus norvegicus (Rat)			1.392	0.394			1.838
Ubiquitin-associated protein 1 - Rattus norvegicus (Rat)		0.271					
UBX domain-containing protein 5			0.532				

- Rattus norvegicus (Rat)							
UDP-glucose 4-epimerase - Rattus norvegicus (Rat)			3.344		0.663		
UDP-glucose 6-dehydrogenase - Rattus norvegicus (Rat)		0.607					
Unc-13 homolog B - Rattus norvegicus (Rat)			1.952		0.742		
Unc-13 homolog C - Rattus norvegicus (Rat)	9.459	1.103	1.288		1.04		
Uncharacterized protein C14orf140 homolog - Rattus norvegicus (Rat)	3.426		2.619	2.314			
Uncharacterized protein C14orf50 homolog - Rattus norvegicus (Rat)				0.407			
Uncharacterized protein C17orf53 homolog - Rattus norvegicus (Rat)		0.532					2.417
Uncharacterized protein C19orf44 homolog - Rattus norvegicus (Rat)							3.242
Uncharacterized protein C1orf55 homolog - Rattus norvegicus (Rat)	5.52				0.657		
Uncharacterized protein C3orf19 homolog - Rattus norvegicus (Rat)			1.75		0.725		2.218
Uncharacterized protein C4orf18 homolog - Rattus norvegicus (Rat)						114.7	
Uncharacterized protein C5orf37 homolog - Rattus norvegicus (Rat)							
Uncharacterized protein C6orf152 homolog - Rattus norvegicus (Rat)	2.807		6.108		0.764		
Uncharacterized protein C8orf37 homolog - Rattus norvegicus (Rat)					0.523		

Uncharacterized protein C8orf45 homolog - Rattus norvegicus (Rat)			2.035	0.374			3.092
Uncharacterized protein C9orf138 homolog - Rattus norvegicus (Rat)	1.761		1.467		0.694	4.17	
UPF0385 protein C1orf82 homolog - Rattus norvegicus (Rat)					1.264		
UPF0415 protein C7orf25 homolog - Rattus norvegicus (Rat)			4.012				
UPF0419 protein C12orf48 homolog - Rattus norvegicus (Rat)		4.666	1.052			6.223	1.502
UPF0428 protein CXorf56 homolog - Pongo pygmaeus (Orangutan)				0.45			
Urinary protein 3 precursor - Rattus norvegicus (Rat)							
Uromodulin precursor - Rattus norvegicus (Rat)	2.957	3.784	4.908	0.6		0.4	3.756
Usherin precursor - Rattus norvegicus (Rat)				2.752	1.353		
Vacuolar protein sorting-associated protein 33B - Rattus norvegicus (Rat)			2.132		0.605		
Vacuolar protein sorting-associated protein 36 - Rattus norvegicus (Rat)	3.854	0.821					4.763
Vang-like protein 2 - Rattus norvegicus (Rat)			3.744				
Vascular cell adhesion protein 1 precursor - Rattus norvegicus (Rat)	5.062						

Vascular endothelial growth factor receptor 2 precursor - Rattus norvegicus (Rat)							1.085
Vascular endothelial growth factor receptor 3 precursor - Rattus norvegicus (Rat)							
Versican core protein precursor - Rattus norvegicus (Rat)			1.936				
Very low-density lipoprotein receptor precursor - Rattus norvegicus (Rat)					0.625		2.278
Very-long-chain acyl-CoA synthetase - Rattus norvegicus (Rat)	0.833		1.1		0.707		1.354
Vesicle transport protein SEC20 - Rattus norvegicus (Rat)			9.55			0.384	
Vesicle-fusing ATPase - Rattus norvegicus (Rat)	11.68	0.375	24.434	0.818	0.799	14.99	30.578
Vesicle-trafficking protein SEC22b - Rattus norvegicus (Rat)							
Vitamin D-binding protein precursor - Rattus norvegicus (Rat)	6.608		4.207	2.259	0.727	14.392	4.773
Vitamin K-dependent protein S precursor - Rattus norvegicus (Rat)	5.987	0.328	2.152	4.109	1.209	7.179	
Voltage-dependent anion-selective channel protein 1 - Rattus norvegicus (Rat)					0.406		
Voltage-dependent L-type calcium channel subunit alpha-1C - Rattus norvegicus (Rat)	10.44		2.889	0.404	0.728		3.707

Voltage-dependent L-type calcium channel subunit alpha-1S - Rattus norvegicus (Rat)	7.414		9.123		0.265		
Voltage-dependent N-type calcium channel subunit alpha-1B - Rattus norvegicus (Rat)					1.303		
Voltage-dependent P/Q-type calcium channel subunit alpha-1A - Rattus norvegicus (Rat)			2.417		0.904		
Voltage-dependent T-type calcium channel subunit alpha-1I - Rattus norvegicus (Rat)			4.159				
Vomeronasal type-1 receptor B13 - Rattus norvegicus (Rat)	3.343						
WAP four-disulfide core domain protein 1 precursor - Rattus norvegicus (Rat)			1.969	0.425			
WAP four-disulfide core domain protein 2 precursor - Rattus norvegicus (Rat)			2.32		0.581		2.795
WD repeat protein 7 - Rattus norvegicus (Rat)	5.43				0.47		
WD repeat protein 78 - Rattus norvegicus (Rat)		1.137		0.591			0.993
Whirlin - Rattus norvegicus (Rat)					0.858		
X/potassium-transporting ATPase subunit beta-m - Rattus norvegicus (Rat)	2.65						
Xaa-Pro aminopeptidase 1 - Rattus norvegicus (Rat)					0.518		

YTH domain-containing protein 1 - Rattus norvegicus (Rat)			1.202				
Zinc finger and BTB domain-containing protein 10 - Rattus norvegicus (Rat)							
Zinc finger and BTB domain-containing protein 24 - Rattus norvegicus (Rat)		0.345			0.834		
Zinc finger and BTB domain-containing protein 38 - Rattus norvegicus (Rat)	13.28						
Zinc finger and BTB domain-containing protein 7A - Rattus norvegicus (Rat)	2.761		2.151	1.359		1.831	
Zinc finger protein 143 - Rattus norvegicus (Rat)							
Zinc finger protein 22 - Rattus norvegicus (Rat)			1.581				
Zinc finger protein 354C - Rattus norvegicus (Rat)							
Zinc finger protein 467 - Rattus norvegicus (Rat)		0.571					
Zinc finger protein 574 - Rattus norvegicus (Rat)	5.574						
Zinc finger protein 652 - Rattus norvegicus (Rat)	5.548		3.387	0.697	1.162	4.621	3.687
Zinc finger protein C6orf113 homolog - Rattus norvegicus (Rat)					0.712		
Zinc finger protein PLAG1 - Rattus norvegicus (Rat)							

Zinc finger UBR1-type protein 1 - Rattus norvegicus (Rat)			1.773	0.243	0.608	3.339	2.452
Zinc-alpha-2-glycoprotein precursor - Rattus norvegicus (Rat)	3.838		2.705		0.772		2.353
Zona pellucida sperm-binding protein 3 receptor precursor - Rattus norvegicus (Rat)	3.661		2.812		0.525		6.362

APPENDIX B

List of potential metabolites that exhibit at least 2-fold increase in intensity after 500 mg/kg dose of D-Serine, at 24 hours

Peak #	Ave Mass	Ave Time	Max Int	Count	Dose P	Time P	DosexTime P
1348	84.04957	1.6133977	762.045	200	0	1.57E-08	4.82E-07
2952	86.08813	1.9950184	322.152	197	0	4.60E-04	0.04143364
2956	86.092575	2.2037451	225.978	169	0	1.86E-05	0.00190426
2447	91.05899	1.7378358	1245.76	200	0	1.14E-04	8.93E-05
2953	91.05901	3.9413092	125.57	195	0	3.46E-04	0.0011826
2384	93.07309	3.9485865	506.406	199	0	3.14E-05	8.40E-04
3609	102.08095	1.0345522	83.038	200	0	9.77E-07	9.59E-04
246	103.05609	3.9495306	2199.88	200	0	2.00E-06	1.75E-04
245	104.10896	1.0066205	458.937	200	0	1.21E-04	0.02520396
2623	107.05372	3.9484622	142.785	200	0	5.85E-05	0.00831197
3166	115.0592	5.048716	76.962	183	0	0.022625038	0.03999975
1146	116.10148	1.0876133	87.0886	200	0	4.03E-06	0.01738393
3057	117.06609	5.052644	133.671	193	0	2.42E-04	0.00248502
335	118.06547	5.0647736	2775.32	200	0	1.63E-10	1.71E-04
96	118.08565	1.0246449	3885.94	200	0	1.08E-05	0.0111196
1715	119.050705	1.7357697	2131.05	200	0	2.35E-04	0.0032236
87	120.07944	3.950787	5869.31	200	0	3.20E-07	3.39E-05
3160	121.06457	1.6877257	84.0507	200	0	2.27E-05	1.08E-06
2505	123.05284	1.730063	1322.37	200	0	2.65E-04	0.00501596
1633	126.05378	3.908415	119.494	200	0	5.05E-04	0.01322353
339	126.06666	1.4237736	415.688	200	0	0.001472629	4.82E-04
1714	130.05061	1.611117	341.849	200	0	2.14E-05	1.14E-05
2624	130.06223	5.0585895	168.101	200	0	3.34E-05	0.01439043
615	132.08096	1.063967	522.497	200	0	0.017004382	0.01344998
3291	133.03955	1.4691375	194.955	196	0	5.54E-08	1.85E-04
1599	136.05174	2.2235155	186.682	200	0	3.14E-04	0.01122707
2385	136.07138	1.7354555	1606.72	200	0	1.37E-04	0.0095505
2677	140.06761	0.99953324	243.559	200	0	0.002632574	0.02398777
2758	142.06387	5.05947	177.375	197	0	3.82E-04	0.00771058
1839	143.07497	1.0600733	155.949	200	0	4.62E-08	0.00161831
3058	143.07764	5.052849	125.57	199	0	8.37E-04	0.0189723
972	144.07207	5.050604	1356.02	200	0	2.39E-09	1.95E-05
3059	144.07764	4.5012546	107.342	200	0	1.41E-04	7.34E-05
2252	145.03825	7.2319155	102.278	198	0	3.12E-06	0.00969727
317	146.0592	5.0647736	4230.38	200	0	1.38E-09	5.99E-04
2682	147.05159	1.7285078	595.694	199	0	6.01E-04	0.01373535
340	151.06102	2.1466618	281.821	200	0	2.23E-04	1.22E-05
1262	152.06493	1.482902	353.452	200	0	9.95E-11	8.92E-04

78	153.06497	2.319414	446.279	200	0	0.002489349	1.44E-04
2225	156.04323	0.9947698	187.716	200	0	7.60E-04	0.0156713
2094	159.05652	4.230849	107.342	200	0	1.06E-06	1.25E-04
2333	159.08954	5.063703	489.528	200	0	1.17E-09	0.00150928
4001	162.05652	1.4188781	46.5823	200	0	0.007677372	0.00959214
4053	163.07487	1.7336693	54.6835	198	0	0.006792427	0.04705726
2841	165.06433	1.7244807	288.026	200	0	9.95E-04	0.00801101
3298	166.07141	3.942531	65.8228	200	0	3.00E-05	0.0017535
1879	170.06596	5.0601916	581.701	200	0	2.08E-05	0.01560745
3430	175.08434	3.9132802	61.7722	200	0	7.99E-04	0.00107124
4071	187.10287	6.009379	71.8987	200	0	0.004184232	0.01542489
1677	192.08253	1.6849494	457.883	200	0	0.006331075	0.03546604
4077	192.10344	2.1228719	250.797	193	0	0.00205122	0.0014501
3062	194.09695	5.0203834	1212.11	200	0	0.004329462	1.40E-04
3627	195.10847	5.040635	199.091	200	0	5.50E-04	0.04580842
2407	198.10469	1.4217672	297.333	200	0	6.03E-05	0.02997687
2371	199.08946	4.972818	91.1392	200	0	2.04E-14	1.67E-04
2996	199.11311	4.160559	225.978	200	0	3.09E-05	0.00742768
775	203.0575	1.0607444	211.501	200	0	0	1.40E-09
1349	205.1051	5.0667257	289.06	200	0	3.79E-05	0.00250376
3614	212.11061	2.388787	114.43	200	0	4.12E-04	0.02738812
824	217.09845	4.9736195	243.559	200	0	0	1.67E-06
2865	218.13692	2.5406518	137.722	200	0	4.34E-05	0.01995755
2138	223.02509	0.88924044	874.362	200	0	0.00438535	0.0144916
2299	224.01292	0.8621526	148.861	164	5.48E-06	1.26E-11	0.00134394
2734	225.01382	0.8708575	137.722	178	5.21E-10	8.35E-11	0.00926157
3064	229.11266	4.9278803	152.911	200	0	1.14E-04	0.00740865
1627	244.06792	5.4081726	666.738	200	0	0.002067628	0.00421152
286	244.11984	1.4711626	1291.03	200	0	2.50E-08	0.00388996
3292	245.97647	0.97839284	99.2405	199	0	6.55E-05	0.02235529
3803	246.11954	1.1250902	61.7722	200	0	8.67E-05	0.00515663
4056	254.10304	4.9240546	95.1899	200	0	5.72E-05	1.08E-04
3186	258.12442	2.5582461	327.323	200	0	4.81E-04	0.03164659
3437	258.12848	2.18375	398.811	200	0	5.01E-14	1.80E-08
2954	258.13034	2.3863103	685.164	200	0	1.14E-14	5.51E-09
3790	260.13477	3.8980846	72.9114	200	0	0.004879952	0.01267771
1111	262.12625	1.4357193	1205.14	200	0	5.28E-09	4.58E-04
2846	265.11646	4.1375427	150.886	200	0	3.67E-05	0.03747946
1924	270.96432	5.0768423	101.266	200	0	0.003171615	0.01441279
2571	276.10596	1.5181682	343.958	200	0	4.13E-09	3.00E-04
2919	276.13696	2.1872766	424.127	200	0	6.84E-05	0.0068766
2248	276.1436	2.423094	583.854	200	0	1.18E-14	6.13E-07
941	290.85052	0.88030577	474.76	200	0	2.48E-06	1.12E-04

1569	292.12	4.1787677	497.967	200	0	9.12E-13	4.16E-05
1234	293.1452	4.088237	105.316	200	0	8.76E-07	0.01008522
4061	294.17352	3.9951518	327.323	199	0	4.41E-05	0.04099479
1598	310.1361	4.2091155	493.748	200	0	3.77E-09	2.05E-04
819	313.07498	11.007765	176.34	200	0	1.22E-10	8.46E-06
3509	316.10217	10.010045	71.8987	200	0	3.93E-10	5.93E-04
2005	328.9573	1.5676808	75.9493	200	0	5.37E-04	0.0104947
1077	331.08923	9.896647	336.63	200	0	5.24E-07	3.60E-04
4062	337.15472	1.0230801	72.9114	138	4.48E-13	0.043607015	0.02447331
3441	349.13193	4.9353266	111.392	200	0	1.45E-08	6.83E-04
236	353.23044	10.610391	253.9	200	0	4.67E-05	0.0043798
2538	355.25616	10.263932	377.714	189	5.45E-10	0	8.45E-07
3461	355.25787	11.972476	302.504	106	2.96E-06	1.25E-07	0.03434393
2625	364.11496	1.0068789	1217.91	181	2.22E-16	0.006640161	0.00353936
2068	366.1883	10.533771	281.821	200	0	0.004689189	4.67E-04
2006	380.09604	0.9676867	2212.87	182	6.35E-12	8.75E-04	0.00681611
3208	386.75034	0.9160272	148.861	200	0	2.56E-08	2.93E-04
1228	423.36447	11.707651	114.43	200	0	1.44E-05	9.13E-05
1957	441.3727	11.708763	98.2278	199	0	3.21E-06	6.88E-06
4065	446.15344	4.3017597	80	197	0	2.16E-08	9.25E-05
2832	462.26868	10.514846	103.291	200	0	5.55E-16	5.45E-06
1596	469.10962	1.5701839	100.253	200	0	5.74E-04	0.00289705
3462	526.16956	1.0365847	76.962	124	6.66E-16	0.019618897	0.00206133
2715	542.14746	1.0126004	181.51	145	5.87E-12	0.001901459	0.01455173
2137	613.4493	7.235638	121.519	191	0	0.030115038	0.00923338

APPENDIX C

List of potential metabolites that exhibit at least 2-fold decrease in intensity after 500 mg/kg dose of D-Serine, at 24 hours

Peak #	Ave Mass	Ave Time	Max Int	Count	Dose P	Time P	DosexTime P
1517	82.07174	1.879631	101.266	197	0	1.82E-07	9.93E-06
601	83.06589	1.180332	235.286	200	0	3.75E-05	2.87E-04
3102	84.07835	6.381208	53.6709	199	0	6.33E-05	0.013596107
2870	94.06844	6.38941	48.6076	191	0	4.75E-12	2.23E-06
2574	95.01995	4.241515	63.7975	194	0	1.22E-06	2.81E-07
283	109.0722	1.134347	433.621	200	0	7.40E-08	2.20E-05
3870	110.0137	0.851168	156.962	124	8.15E-07	2.31E-13	4.34E-04
860	110.0624	5.491352	179.443	200	0	6.60E-06	0.01184042
2836	112.053	1.869181	90.1266	184	0	3.61E-07	4.26E-08
859	112.0538	4.212901	342.904	197	0	5.61E-04	8.53E-04
1489	112.0774	2.505941	86.0759	194	0	3.76E-04	7.80E-06
2410	115.0873	2.502329	60.7595	185	0	1.76E-04	3.17E-05
3953	116.0647	5.986458	77.9747	200	0	1.53E-05	0.039489854
2526	122.0253	2.763338	72.9114	198	0	1.05E-05	1.14E-09
2793	122.06	6.396854	100.253	197	0	1.13E-09	8.62E-05
2242	123.0537	7.216255	71.8987	199	0	0.0022573	0.037158746
1323	124.0452	1.948567	95.1899	199	0	4.11E-07	0.009164446
156	124.0858	1.183827	1889.49	200	0	5.99E-07	1.16E-04
4161	125.0732	7.215042	53.6709	193	0	0.0136409	0.008364056
1117	126.0584	4.503311	98.2278	200	0	6.35E-08	8.05E-05
363	126.0639	1.627348	2188.19	200	0	2.53E-08	1.65E-05
1059	127.0844	2.735664	150.886	198	0	7.11E-15	2.32E-14
1032	128.0716	2.737329	168.101	199	0	2.35E-13	6.24E-14
248	130.0734	1.396551	481.089	200	0	0.01206816	0.023777328
2001	131.055	7.964372	85.0633	198	0	8.61E-06	0.004592696
522	134.0938	6.389249	238.388	200	0	8.23E-09	0.002140677
986	134.0943	6.949552	121.519	200	0	7.53E-07	9.43E-05
457	134.0962	7.609713	368.22	198	0	1.29E-07	4.24E-05
3759	135.1134	9.463046	56.7089	182	0	1.10E-04	0.005882433
639	138.0887	4.582331	241.49	200	0	6.52E-07	2.04E-04
2991	140.0675	1.482524	151.899	200	0	5.79E-08	0.001136139
1068	140.0832	1.4433	270.446	200	0	2.47E-09	0.008284124
2155	141.0988	1.883557	67.8481	186	0	3.93E-05	8.44E-05
3411	142.0581	1.954977	164.051	200	0	2.83E-08	1.42E-04
985	145.0431	5.894676	97.2152	200	0	8.66E-06	0.041481055
3972	145.0448	5.893686	97.2152	200	0	0.02916043	0.041136254

1974	147.0882	6.389411	53.6709	200	0	2.08E-06	0.002860708
807	148.085	1.181704	124.557	200	0	1.62E-07	7.84E-04
382	148.1073	6.387697	510.656	199	0	3.04E-10	2.73E-04
3774	149.0951	7.991058	55.6962	191	0	2.21E-07	9.33E-04
2867	149.0974	9.340841	65.8228	193	0	7.77E-08	3.52E-06
205	150.0743	1.41976	1241.12	200	0	0.01661612	0.002756738
3329	150.0893	7.894943	45.5696	184	0	4.81E-04	0.039200928
1750	151.0745	9.378783	78.9874	195	0	4.35E-06	0.002687052
3847	151.1036	7.940842	62.7848	192	0	2.15E-07	1.30E-06
599	153.066	1.12668	202.193	200	0	9.73E-04	0.009992168
3484	153.1273	9.747367	65.8228	190	0	3.83E-04	0.026360665
3154	154.0754	4.213249	73.9241	194	0	3.11E-06	2.88E-05
883	158.0958	6.387123	106.329	200	0	5.56E-08	0.005902311
1145	161.1029	6.388011	75.9493	199	0	4.52E-08	1.56E-05
1388	161.1061	7.612068	74.9367	197	0	5.42E-05	0.005683868
2885	162.0548	5.98512	1595.11	200	0	5.79E-04	0.021121904
1144	162.0909	7.611351	133.671	196	0	5.75E-07	0.014492168
4159	164.0763	3.133338	56.7089	172	0	1.65E-04	0.040840115
2508	165.0891	9.948325	61.7722	192	0	5.31E-04	0.009138503
1601	165.0944	5.744429	97.2152	199	0	4.45E-11	2.96E-07
1200	165.0953	5.212597	124.557	200	0	6.13E-06	0.02535239
1592	166.0714	3.760973	150.886	193	0	2.90E-04	6.46E-05
313	166.0965	1.18003	427.292	200	0	8.62E-06	0.008922817
1998	166.1064	8.147736	162.025	193	8.88E-16	2.03E-08	0.029034676
1932	167.0983	7.477122	69.8734	198	0	8.49E-07	0.038834542
1973	167.114	4.793782	100.253	200	0	1.23E-06	0.003202127
565	168.1069	1.129542	251.832	200	0	4.98E-05	8.53E-04
1646	169.0957	1.881685	68.8608	187	0	2.33E-05	7.95E-04
3201	170.0742	6.387216	44.557	200	0	1.66E-06	0.046616133
3349	170.0811	1.883401	107.342	199	0	4.37E-06	0.005605498
202	170.0915	1.171967	559.096	200	0	6.41E-06	0.001095396
3350	172.0451	6.530146	92.1519	200	0	0	3.00E-11
1253	172.0458	6.147384	103.291	200	0	1.19E-04	5.22E-05
1327	172.106	2.039606	87.0886	200	0	0.00481446	0.007324291
1114	173.0922	1.605273	82.0253	198	0	8.69E-04	0.04077835
983	173.0927	2.737249	109.367	198	0	5.60E-11	1.11E-08
636	174.0922	4.988294	187.716	200	0	2.43E-05	0.004640492
570	174.0925	7.225359	250.797	200	0	2.61E-10	2.37E-04
804	174.0929	6.387764	150.886	200	0	1.32E-07	0.003652974
1041	175.1084	2.044306	85.0633	200	0	0.0183291	0.033589404
267	175.1218	6.386003	930.072	200	0	9.09E-11	5.81E-05
2408	176.0183	1.023729	63.7975	200	0	1.08E-04	0.034774344
982	176.0954	8.287018	92.1519	198	0	2.10E-04	0.046911836

890	177.1239	7.728504	108.354	199	0	1.84E-06	0.003678584
1797	179.0612	7.084031	68.8608	200	0	3.21E-04	0.028510923
2747	179.0672	1.212197	141.772	200	0	1.83E-05	7.79E-04
2708	180.0841	2.734522	55.6962	191	0	1.23E-10	1.38E-04
312	180.0877	4.544973	646.286	200	0	1.61E-04	0.00399717
1901	180.1009	4.782151	174.272	200	0	4.04E-06	0.006994803
1408	181.0862	9.338377	87.0886	199	0	2.07E-07	4.60E-04
947	181.1213	9.540705	118.481	199	0	6.53E-09	0.004010064
1985	182.1066	5.734355	66.8354	199	0	1.94E-04	0.002047299
1731	182.1254	6.603002	155.949	198	0	2.22E-16	1.79E-07
483	182.1269	6.869908	477.925	200	0	0	3.29E-07
2700	182.9582	0.836557	186.682	126	1.43E-05	4.85E-14	3.16E-04
1165	183.1054	9.491188	122.532	197	0	1.74E-07	0.002940896
670	183.111	5.209004	139.747	200	0	3.05E-08	0.03452555
564	185.1266	4.792522	152.911	200	0	2.49E-07	3.70E-04
832	187.1061	1.883638	136.709	197	0	8.62E-07	6.35E-04
2149	188.1035	8.666565	68.8608	198	0	2.48E-05	0.024432195
2064	189.0762	1.916698	71.8987	194	0	6.06E-05	0.04769794
677	189.0978	6.697059	132.658	200	0	1.76E-06	1.01E-04
1003	190.1185	7.22456	119.494	199	0	2.23E-10	0.011714504
481	191.1167	6.385151	229.081	200	0	6.87E-09	5.03E-04
3772	192.098	4.493568	1811.57	200	0	3.00E-05	1.93E-05
1217	192.1009	6.946087	150.886	200	0	4.07E-05	0.006665939
120	192.1011	4.482733	1849.23	200	0	7.86E-08	9.64E-05
633	192.1018	7.897367	273.548	200	0	1.94E-07	0.021569889
381	192.1031	6.385781	334.562	200	0	2.28E-08	0.00262377
1070	193.1026	7.969515	105.316	200	0	6.82E-08	8.69E-06
563	194.0941	1.147416	160	200	0	3.38E-06	0.009562996
408	194.102	4.21834	692.852	199	0	0.03241124	0.006272961
1675	194.1174	3.434815	95.1899	199	0	3.12E-12	1.47E-06
806	194.1881	6.672429	149.873	196	0	2.23E-09	0.001255542
1571	194.1891	6.069194	99.2405	197	0	1.03E-07	1.27E-04
360	195.1101	4.86342	258.036	200	0	1.79E-07	0.003326612
1470	195.1101	7.894579	119.494	200	0	1.42E-06	0.032456376
2903	195.1315	7.727717	83.038	200	0	2.05E-07	0.007837604
1930	196.1541	6.564489	189.784	195	0	3.16E-07	0.04846565
713	197.1264	7.609674	241.49	200	0	3.60E-07	0.002373294
3312	198.934	0.842971	262.173	147	2.04E-10	2.22E-16	1.26E-04
613	200.1137	5.578102	224.944	200	0	0.00265982	0.004871853
1832	200.1579	5.34229	98.2278	200	0	7.47E-11	0.01617194
1552	202.0963	6.550367	107.342	200	0	0	2.43E-08
1620	203.1489	2.046122	88.1013	200	0	0.04259948	0.006855804
961	205.124	6.383493	77.9747	200	0	2.14E-08	0.003401264

786	207.1034	7.832212	94.1772	200	0	4.80E-07	0.003464855
2674	207.1104	4.187753	56.7089	200	0	4.48E-05	0.045043375
760	209.118	9.338763	124.557	200	0	9.33E-07	0.002224925
561	209.1238	6.384263	136.709	200	0	8.45E-08	1.39E-04
435	209.1245	5.405905	126.582	200	0	3.46E-05	0.003098649
293	210.1121	4.483182	387.207	200	0	5.09E-07	3.00E-04
1822	210.1819	7.594966	103.291	194	0	1.58E-04	0.003397271
1911	211.1266	6.993475	173.238	200	0	4.05E-06	0.002644787
1321	211.1271	4.481213	131.646	200	0	2.34E-04	0.042218514
63	212.1025	1.129993	2018.06	200	0	2.05E-04	0.021974765
1574	212.1252	4.996415	66.8354	200	0	3.31E-05	0.007567061
785	214.1789	6.851584	137.722	200	0	2.43E-05	0.001689013
3844	215.1008	2.731668	47.5949	192	0	0.00153604	8.15E-05
2042	215.1142	1.208049	495.857	197	0	3.10E-05	5.73E-04
1979	218.0433	8.727408	48.6076	199	0	2.31E-06	0.017820721
1252	218.0857	6.618119	82.0253	200	0	2.73E-07	0.003308022
1163	218.9928	0.993579	146.835	195	0	4.56E-08	0.039913807
379	219.1146	6.385379	205.296	200	0	1.18E-09	9.29E-04
3670	219.1269	8.117483	145.823	200	0	0.00529885	0.039888907
1871	220.104	6.379259	81.0126	200	0	2.63E-06	0.03230807
560	221.1153	9.53875	203.228	200	0	8.68E-09	0.00398818
2890	223.1084	8.174742	59.7468	200	0	5.32E-04	4.97E-04
3922	223.1945	5.644831	59.7468	186	0	0.00210771	0.009156385
2019	224.199	8.301798	131.646	190	0	1.68E-04	0.020929648
1920	225.1005	6.472523	112.405	200	0	7.66E-06	0.010465914
559	226.1529	7.113217	458.937	200	0	0	3.85E-13
1486	228.1899	7.595055	109.367	197	0	6.96E-04	0.026423534
2018	231.1377	9.747438	114.43	199	0	0.00197979	4.29E-04
93	231.1702	1.22966	1252.73	200	0	0.0012249	0.016126994
791	233.1043	7.518303	169.114	200	0	0	8.36E-06
3258	233.1305	8.721536	63.7975	200	0	6.02E-06	0.00131833
895	234.1434	8.133548	177.375	200	0	0	4.44E-06
701	234.1444	7.196075	282.855	199	0	0	2.86E-05
302	234.9703	0.987404	591.388	200	0	4.30E-08	0.013327611
2380	235.1152	5.10968	130.633	200	0	2.16E-06	0.025421407
2262	236.0499	7.691745	61.7722	200	0	5.74E-06	4.16E-04
1081	236.063	5.159886	85.0633	200	0	9.11E-07	0.038371556
3572	236.1037	2.34572	84.0507	187	0	4.78E-04	0.016472321
2521	236.1377	3.442836	56.7089	186	0	0	4.84E-06
1614	236.9076	0.865315	298.367	197	0	1.48E-09	0.015688123
378	237.1229	6.384716	231.149	200	0	1.41E-06	0.001768055
1366	237.1348	7.909548	158.987	200	0	3.35E-06	0.026425557
1554	239.0804	8.311657	134.684	200	0	3.57E-04	0.036871925

2116	239.1028	3.529314	60.7595	191	0	4.34E-04	0.012828258
458	239.1179	6.947756	158.987	200	0	3.95E-04	0.008094547
464	239.1191	8.28712	140.76	200	0	4.44E-07	0.022615101
427	239.1347	7.617037	192.886	200	0	1.66E-05	0.028862681
3969	240.0742	9.80442	51.6456	192	0	7.09E-06	0.008690995
1421	240.1842	6.496102	107.342	200	0	2.20E-07	9.65E-04
3119	242.0509	4.363274	103.291	200	0	4.95E-04	0.037389714
1432	242.207	8.300689	150.886	199	0	2.63E-05	0.015042175
1506	243.1376	9.871283	87.0886	200	0	0.00103742	0.006416587
579	245.1759	4.24893	329.391	200	0	1.15E-06	0.001607696
1942	247.0113	8.740284	52.6582	197	0	1.44E-06	0.044751056
1629	247.1292	8.342567	81.0126	200	0	3.35E-07	0.002690232
558	247.1609	1.505006	190.818	200	0	1.00E-10	0.005996592
1697	248.1162	7.109869	768.635	200	9.99E-15	1.51E-05	0.005763828
486	248.1498	1.914797	521.42	198	0	1.89E-04	0.012446946
3786	248.8812	0.921797	87.0886	198	0	8.55E-14	9.86E-06
3324	249.0726	11.29032	66.8354	191	3.33E-16	3.40E-07	0.002618771
1862	249.1247	7.134144	167.089	200	0	5.39E-04	0.045656957
3589	249.1348	8.464188	77.9747	200	0	0.01516124	0.048037644
3010	249.1391	7.904149	72.9114	200	0	0.00592884	0.00391262
2929	250.1133	7.869158	61.7722	199	0	1.70E-05	0.013976174
444	251.1392	6.380563	200.125	200	0	8.96E-08	0.016096253
595	251.1595	7.490368	158.987	200	0	0.02547067	0.002646805
414	252.0754	1.938182	251.832	200	0	1.98E-08	2.23E-04
3314	252.1055	7.307737	286.992	200	1.11E-16	0.00918034	0.008964345
849	252.1269	6.382228	91.1392	200	0	0.00811814	0.025567316
3564	252.1314	7.941877	70.886	199	0	0.0017526	0.018013338
3691	252.1502	8.875059	61.7722	196	0	4.33E-11	0.004753199
684	252.1511	7.374473	286.992	200	0	1.04E-08	0.001550065
355	253.1176	4.194489	199.091	200	0	0.00130969	0.040721647
1071	253.1231	7.800101	118.481	200	0	0.01406822	0.034834173
594	254.1033	1.474168	339.739	200	0	1.08E-09	0.003187432
901	254.1116	2.738956	109.367	198	0	1.83E-08	1.83E-04
115	255.0644	8.652161	7633.7	200	0	1.95E-10	0.007036682
1049	255.1065	7.908737	487.418	200	0	3.34E-06	8.55E-04
1069	255.1129	2.531804	125.57	200	0	3.27E-04	1.30E-04
463	255.1169	7.898853	459.992	200	0	9.76E-04	0.018062903
242	255.1336	4.482554	798.289	200	0	5.45E-07	1.88E-04
1624	256.0673	5.645192	70.886	200	0	0.01269597	0.003608901
1819	256.0999	4.33928	98.2278	200	0	0.00241038	0.01985731
2997	256.1737	5.782792	65.8228	200	0	0	4.84E-06
1175	256.8175	0.966782	84.0507	195	0	6.62E-04	0.009178686
3032	257.0999	6.402834	119.494	200	0	0.00819096	0.017379576

1854	258.1404	7.080878	91.1392	200	0	7.10E-04	0.026981061
1140	258.1601	5.239361	162.025	200	0	4.48E-07	3.23E-04
515	258.2048	6.496241	193.921	200	0	5.20E-09	0.001146365
1746	259.1494	1.624595	269.412	199	0	8.57E-10	0.01688762
1428	259.1585	1.959265	257.002	184	0	1.25E-08	0.03404577
469	259.1882	5.202804	423.072	200	0	1.49E-04	0.0074806
889	260.0912	1.298003	458.937	200	0	2.29E-06	0.006945851
3197	260.1445	1.954606	61.7722	188	0	4.35E-09	0.018538835
3459	260.7989	0.963729	69.8734	198	0	7.17E-05	0.022060083
3153	261.1462	9.864613	93.1646	200	0	0.00855232	0.004170218
2304	263.0992	9.126825	83.038	200	0	1.11E-16	1.29E-08
1772	263.1505	9.436996	57.7215	200	0	2.71E-04	0.019777913
1287	265.086	7.083323	109.367	200	0	5.22E-08	0.009852578
3014	265.0996	6.774134	77.9747	200	0	0.00105432	0.003162965
1914	265.1091	8.064269	114.43	200	0	1.53E-10	3.72E-04
475	265.1203	5.532954	174.272	200	0	7.04E-07	0.032268863
834	265.1528	2.494783	110.38	197	0	4.20E-04	0.025824979
1664	266.1295	7.116216	812.567	200	8.88E-16	1.55E-05	0.002903193
1057	266.1441	1.512797	105.316	194	0	2.19E-14	1.29E-04
978	266.1453	4.44121	96.2025	200	0	7.14E-07	0.009695804
2374	267.1215	9.498182	69.8734	195	0	4.49E-07	1.78E-04
474	267.1227	6.49377	171.17	200	0	9.17E-04	0.024412867
2321	267.1668	9.259799	55.6962	199	0	2.76E-07	0.001455276
2017	268.1246	1.635555	64.8101	199	0	1.06E-08	0.048069686
530	268.1607	4.04893	152.911	200	0	2.06E-07	0.010324259
2697	269.0606	9.77642	86.0759	187	0	0.03665351	0.025701463
2402	269.0734	7.541782	113.418	200	0	0.00790502	0.027808955
950	269.0855	8.619255	1520.83	200	5.66E-15	3.11E-15	5.06E-10
3561	269.0868	8.6197	1520.83	200	1.05E-14	2.11E-15	4.22E-10
1438	269.1251	1.477689	191.852	200	0	6.96E-07	0.001309991
320	269.1362	6.708867	508.515	200	0	3.74E-05	0.018969472
4148	269.1419	6.314859	99.2405	200	0	1.31E-07	3.97E-04
2862	270.0815	2.737372	60.7595	198	0	7.32E-07	2.32E-04
2048	270.1509	7.812868	206.33	199	0	1.12E-05	0.009814831
848	270.171	4.579493	107.342	200	0	0	9.89E-07
375	271.0613	9.77354	1466.28	199	0	1.50E-06	0.040049452
376	271.063	5.89553	554.79	200	0	1.66E-08	8.26E-04
2861	271.1861	6.654817	52.6582	199	0	2.18E-04	0.007104258
942	272.0752	5.89431	112.405	200	0	2.87E-09	0.002040155
3630	272.1077	6.320119	61.7722	200	0	8.30E-05	0.007539699
571	272.1149	1.470788	885.968	199	0	2.44E-10	0.003950633
3478	273.0831	9.78595	61.7722	191	0	1.90E-08	0.007876894
2146	273.1614	4.194197	120.506	200	0	1.27E-09	0.035081744

2461	273.1742	3.288909	71.8987	174	0	2.56E-07	0.048233405
1385	273.2048	6.681249	100.253	195	0	1.14E-06	0.010835592
1012	274.1222	1.522104	116.456	199	0	8.25E-12	5.99E-04
328	275.1274	10.65572	749.964	200	0	4.61E-05	0.00606633
4101	275.14	1.647959	51.6456	198	0	4.42E-04	0.04907528
2472	276.1473	6.524519	52.6582	200	0	3.07E-05	0.025301708
1139	277.1339	7.916038	81.0126	200	0	1.18E-04	0.019576667
4029	277.1355	7.913386	81.0126	200	0	6.26E-05	0.02086236
3736	277.1445	9.602552	59.7468	199	0	5.12E-07	0.0014331
3653	277.1639	9.880779	54.6835	197	0	0.00103595	0.012816134
1227	278.1068	5.666903	271.48	200	0	4.64E-11	1.62E-06
1759	278.1364	6.954777	59.7468	200	0	0.00380913	0.028926052
3857	279.1206	7.186102	95.1899	200	0	0.0076207	0.005077565
241	279.135	4.483135	503.241	200	0	5.87E-07	0.005183413
1853	279.1643	3.977053	147.848	199	0	6.20E-11	9.30E-05
557	279.1686	4.290698	426.237	200	0	3.05E-05	0.019311665
3873	280.1139	7.839171	41.519	200	0	7.94E-05	0.035422806
3763	281.1471	3.421255	50.6329	176	0	0.00159137	0.01604537
1080	281.1479	3.85288	142.785	200	0	3.89E-06	0.006305561
1195	281.1486	2.929985	103.291	189	0	1.79E-08	7.17E-06
424	281.1505	4.050181	304.572	200	0	4.42E-06	0.008909932
789	282.0125	8.732165	330.425	200	0	2.22E-05	0.03309411
556	282.1115	1.438196	260.104	200	0	0.00490079	0.01313623
1026	282.1478	3.441802	116.456	193	0	6.66E-16	1.69E-06
2723	283.0856	8.415346	138.734	200	0	8.06E-10	2.59E-05
44	283.1179	6.643526	745.57	200	0	9.88E-05	0.013864497
141	283.1288	4.317322	340.794	200	0	3.33E-12	2.96E-04
3194	283.1365	3.803341	126.582	200	0	1.23E-06	5.49E-06
2375	285.0879	7.578028	281.821	200	0	0	0
1491	285.0998	1.923426	77.9747	200	0	8.01E-07	0.00550598
2002	285.1116	9.710732	357.671	195	1.11E-16	6.63E-13	3.26E-09
2706	285.152	3.196313	51.6456	186	0	2.46E-05	7.18E-04
727	285.1546	1.641498	144.81	198	0	3.63E-11	0.005928948
461	285.1559	3.679545	308.708	199	0	5.27E-05	0.002442291
405	285.1766	5.71102	322.152	200	0	9.81E-06	0.025763521
1622	286.103	6.209599	116.456	200	0	0.0045174	0.00115407
1529	286.1361	4.327315	147.848	200	0	1.57E-04	7.22E-04
2075	286.1406	4.109687	106.329	200	0	0.00319868	0.042585474
1202	286.167	5.710187	78.9874	200	0	0.00329696	0.030456701
2401	286.1718	2.935391	72.9114	183	0	2.26E-04	0.001610224
2279	286.2089	7.251373	71.8987	197	0	7.98E-04	0.038521674
959	286.2325	7.975503	113.418	199	0	5.73E-10	4.42E-05
3838	286.9654	3.138039	56.7089	190	0	6.97E-05	0.002198703

2963	287.1318	7.127036	70.886	200	0	3.25E-04	0.049395625
1459	287.1414	5.564217	97.2152	200	0	0.0166768	0.024267878
2016	287.1773	5.370036	117.468	198	0	4.01E-10	0.003854608
1458	287.1953	9.600143	86.0759	198	0	0.0015024	0.042855375
3652	288.1041	9.369199	51.6456	191	0	3.26E-08	2.97E-04
1232	288.1805	7.253818	89.114	200	0	0.00212802	0.048536204
1054	288.1853	4.32545	83.038	199	0	1.16E-05	0.007581507
645	289.1505	1.93868	186.682	197	0	4.54E-05	0.002429122
3353	290.1079	10.15167	65.8228	195	0	0.00110081	0.002366169
1570	290.1239	1.136442	503.241	200	0	1.28E-14	9.99E-04
431	290.1256	1.469668	1537.08	199	0	5.44E-11	0.001904756
1485	290.1258	1.711152	930.072	199	0	1.09E-07	0.041166343
2696	290.1628	7.216478	68.8608	200	0	6.30E-06	0.013688089
3882	291.1022	9.107613	67.8481	198	0	0	6.50E-07
404	291.1221	7.986905	216.671	200	0	0	3.96E-07
3144	291.1335	4.705237	54.6835	200	0	0.0061793	0.011250374
2352	292.1276	4.641387	57.7215	200	0	9.34E-05	4.00E-04
907	293.1545	5.166946	102.278	200	0	9.82E-09	2.91E-05
627	294.1456	1.413806	157.975	199	0	8.85E-06	0.008684828
614	294.1729	4.190084	219.774	200	0	4.21E-04	0.010693601
299	295.1287	4.794546	238.388	200	0	2.40E-08	1.33E-04
1151	295.1289	3.228193	111.392	194	0	1.04E-08	8.26E-05
3464	295.152	7.943456	107.342	200	0	2.93E-06	0.047066905
1634	295.1573	6.588158	82.0253	200	0	0.02000879	0.010601065
2251	296.148	4.283344	69.8734	200	0	0.0010581	0.04917724
682	297.1041	6.340299	137.722	200	0	0.0236474	0.011092422
43	297.1377	4.485386	16437.4	200	0	2.63E-06	0.003580101
608	297.1447	2.141138	173.238	196	0	1.79E-06	0.01618642
3083	297.1576	5.581934	155.949	200	0	0.00243331	0.046325322
2246	297.173	8.675628	120.506	199	0	7.33E-05	0.002082923
2128	298.1086	7.32613	80	200	0	5.65E-08	0.02191522
42	298.1497	4.48502	2094.68	200	0	9.64E-06	0.02473817
3498	299.1411	8.52016	67.8481	200	0	1.57E-06	0.003861183
1235	300.0772	8.413127	148.861	197	0	1.19E-07	0.003004497
2899	300.1202	8.472988	148.861	197	0	3.33E-16	9.12E-07
644	300.1782	6.167072	177.375	200	0	1.45E-06	0.048142023
999	301.0795	9.01977	443.115	199	0	7.13E-12	2.71E-04
3767	301.0907	9.025102	443.115	200	0	4.46E-08	1.33E-05
616	301.1723	6.558423	1133.18	200	0	8.84E-08	0.04424021
2926	303.1189	6.727721	74.9367	200	0	1.11E-05	0.024030639
2399	303.1545	3.872179	58.7342	199	0	0.00728912	0.001725974
3924	303.2199	6.610787	328.357	200	0	8.58E-07	1.60E-04
552	303.225	6.61599	328.357	200	0	2.45E-08	3.73E-04

1391	304.8944	0.864969	179.443	197	0	3.57E-14	0.001111823
3717	305.1741	5.742145	109.367	200	0	5.55E-09	0.029257499
998	306.0559	6.125873	87.0886	200	0	1.13E-06	0.012108226
2860	307.1052	9.789315	54.6835	192	0	0.02199194	0.04454174
3692	307.1068	7.572584	74.9367	200	0	0	3.58E-11
1281	307.1095	7.141874	104.304	200	0	3.36E-04	0.007204766
2830	307.1606	6.657445	84.0507	200	0	5.72E-06	0.002158898
1512	307.1888	6.164506	68.8608	199	0	1.11E-07	0.003072259
626	308.0357	5.041912	139.747	200	0	1.45E-05	0.043108687
800	308.1218	3.901486	70.886	198	0	2.72E-05	0.008564225
921	309.1015	9.107005	143.797	200	0	0	4.33E-12
795	309.1631	8.016076	99.2405	200	0	1.19E-06	0.035364624
1304	311.1766	7.260455	143.797	200	0	3.33E-04	0.028732821
3345	311.1773	7.263779	143.797	200	0	0.01322343	0.006642388
1751	312.0913	2.279359	132.658	192	0	6.29E-12	6.55E-04
1533	312.128	9.443973	153.924	199	0	4.19E-13	0.001583421
2602	312.1735	5.628767	103.291	200	0	1.36E-13	1.34E-04
3984	313.0915	9.317362	57.7215	197	0	1.49E-06	0.001502415
511	313.1403	4.271491	155.949	200	0	1.38E-05	0.005478439
1707	314.0641	6.643066	99.2405	200	0	8.87E-04	0.011214698
3687	314.1394	9.527211	53.6709	193	0	1.05E-11	0.001848737
2537	315.1042	9.087399	75.9493	198	0	1.11E-16	5.48E-06
2512	315.203	7.070087	100.253	198	0	4.40E-06	0.010268354
3925	315.2222	10.0455	73.9241	196	0	0.04885681	0.01570113
239	316.1755	4.744916	336.63	200	0	6.59E-04	0.018284535
3663	317.1304	8.101813	51.6456	200	0	3.82E-05	0.028884392
2528	317.1404	5.580112	71.8987	200	0	0.00325486	0.015756717
2310	317.1493	9.294308	63.7975	198	0	2.05E-10	0.007038879
3748	319.107	4.445958	306.64	200	0	7.74E-06	0.005731061
3402	319.1272	9.459889	53.6709	193	0	3.74E-08	0.005683718
291	319.1301	6.950586	641.98	200	0	1.28E-04	0.012172558
683	319.1953	6.666838	305.606	200	0	3.31E-05	0.019207763
2166	320.7391	0.961455	83.038	197	0	1.63E-04	3.12E-04
455	320.8711	0.867169	336.63	200	0	5.23E-11	0.025917998
2188	322.1037	3.86194	66.8354	197	0	0.00145986	0.00796749
1718	323.0496	8.727001	63.7975	200	0	6.19E-06	0.009824898
1612	323.1777	9.567678	63.7975	194	0	2.52E-04	9.45E-04
3454	324.174	6.135322	67.8481	199	0	0.00772613	0.022533782
2267	324.1797	4.9685	100.253	200	0	0.02581183	0.008452133
1779	324.1866	4.038514	111.392	198	0	3.99E-06	1.35E-04
817	324.1881	7.220897	131.646	196	0	3.51E-06	0.030546734
930	325.0927	3.543807	88.1013	195	0	3.98E-09	0.001647161
2078	325.1217	5.579131	60.7595	200	0	2.15E-05	0.024244923

1851	325.1391	4.836792	84.0507	200	0	4.77E-07	4.49E-04
3731	325.1406	6.80168	66.8354	200	0	1.86E-04	0.007246942
1280	325.1959	9.255278	125.57	199	0	1.97E-08	2.59E-04
422	326.0435	5.04169	295.265	200	0	1.68E-05	0.02331696
2047	326.1511	4.123982	283.889	199	0	1.53E-06	5.97E-04
976	326.1698	4.717348	107.342	200	0	1.34E-04	0.011687511
696	326.1946	9.491132	235.286	193	0	5.13E-08	0.00787954
664	326.1947	6.978779	301.47	200	0	2.36E-07	5.97E-04
1929	326.8519	0.887289	86.0759	196	0	9.09E-12	0.002885979
663	327.1566	4.710072	172.204	200	0	1.02E-05	0.009480233
4143	328.0374	5.041606	44.557	199	0	0.00132273	0.01548464
695	328.1304	6.550117	84.0507	200	0	2.31E-12	3.02E-05
1383	328.1715	5.54839	86.0759	200	0	1.78E-06	0.02158133
2589	328.1982	6.472564	83.038	200	0	1.98E-04	0.042737555
509	328.2095	7.4768	623.681	200	0	1.38E-07	0.017182367
585	328.2101	6.945892	279.753	200	0	5.82E-04	0.004276928
1078	329.0748	8.607815	187.716	196	0	8.79E-04	0.018683426
3634	329.1798	6.939492	82.0253	200	0	0.0104206	0.026303442
1121	329.1848	6.941574	112.405	200	0	0.00109878	0.008394527
612	330.0621	2.320891	430.456	195	0	0.04224042	0.024789289
3036	330.1104	3.604917	70.886	160	0	7.72E-08	0.011604518
906	330.2211	6.966847	103.291	199	0	6.06E-06	0.007126417
472	330.2275	8.529066	272.514	200	0	3.40E-06	0.02209467
876	331.0901	8.121133	162.025	199	0	4.60E-13	6.71E-04
1850	331.0962	10.65406	95.1899	195	0	9.78E-04	0.020743556
3099	331.1742	7.294017	56.7089	200	0	9.96E-05	0.04526835
3580	331.2047	8.158123	70.886	199	0	0.00200908	0.03913728
1643	332.1043	6.381233	194.955	200	0	3.15E-06	0.039720267
2077	332.8442	0.898955	77.9747	200	0	3.03E-07	0.03351522
3023	333.1509	7.064424	51.6456	200	0	0.03979385	0.020499358
2069	335.0461	7.952144	92.1519	193	0	0	8.82E-09
546	335.1044	6.951566	164.051	200	0	5.77E-07	0.004010085
2259	335.1517	7.772254	59.7468	200	0	7.71E-12	0.003905345
584	336.1575	7.012736	137.722	199	0	2.54E-06	0.011070186
2834	337.1228	8.428513	91.1392	199	0	0.04978605	0.036161155
3926	337.123	4.560759	50.6329	200	0	0.04783253	0.04368352
3225	337.1421	7.762109	145.823	200	0	6.86E-10	3.09E-04
2430	338.1726	5.610379	58.7342	200	0	3.11E-04	0.025897559
1755	339.1367	8.129092	94.1772	200	0	0.03984672	0.013008633
1665	340.1601	1.693141	148.861	199	0	4.46E-11	0.002865137
3369	341.1382	6.981851	147.848	200	0	5.15E-04	0.039200015
1895	341.2009	7.926983	78.9874	199	0	8.33E-09	1.66E-05
1286	342.2199	8.446283	90.1266	199	0	2.32E-04	0.042456917

1728	344.1383	6.240004	122.532	200	0	1.11E-16	5.86E-06
3677	344.8668	0.854239	138.734	188	0	1.96E-05	0.001577911
508	345.1533	6.973118	105.316	200	0	2.63E-04	0.049723446
2775	346.2046	6.73258	66.8354	200	0	3.18E-04	2.16E-04
1894	346.2138	5.492053	70.886	199	0	8.60E-05	0.006338327
1864	347.1661	6.743651	55.6962	200	0	5.52E-06	5.58E-04
3238	348.1857	7.285471	52.6582	200	0	2.98E-05	0.029778898
843	348.1866	7.49011	102.278	198	0	5.72E-05	0.01456632
1023	348.233	6.206296	138.734	192	0	4.52E-07	0.01807224
934	349.1511	8.3892	109.367	200	0	0.00411965	0.002817952
2021	350.1121	6.299208	133.671	197	0	1.03E-07	0.019070394
2204	351.1299	6.591806	54.6835	200	0	7.75E-08	0.007317717
1468	351.1992	8.491012	85.0633	200	0	0.02050386	0.006576315
1630	352.1756	4.180418	90.1266	196	0	2.85E-08	0.049724158
2143	352.2072	7.77219	181.511	198	0	1.09E-08	3.66E-04
440	352.2107	7.416805	410.414	200	0	3.32E-05	0.005966981
1362	353.1647	5.537796	107.342	200	0	4.80E-05	0.02377199
2603	353.1754	7.780031	60.7595	200	0	6.01E-05	0.037571445
2031	354.1695	5.653268	71.8987	200	0	1.55E-04	0.001666644
2090	354.1952	3.904833	152.911	191	0	3.55E-09	0.008616385
3745	354.2224	8.636998	82.0253	197	0	1.43E-06	0.009408149
1135	354.2252	5.887998	110.38	199	0	2.70E-11	0.003875969
138	354.2268	7.934926	3816.1	200	0	4.72E-07	0.005476716
399	354.2281	7.194203	559.096	200	0	2.61E-04	0.016399365
1021	355.2113	7.19384	171.17	200	0	0.01064284	0.02522596
1892	356.1225	9.37962	114.43	196	0	7.25E-10	0.002857298
685	356.2124	6.460881	138.734	200	0	1.44E-04	1.91E-05
2193	356.2405	9.561444	78.9874	186	0	1.14E-09	4.29E-07
3833	356.2406	10.10033	72.9114	188	0	4.39E-04	0.00677486
111	356.2409	7.726426	4092.29	200	0	3.23E-08	0.004838304
3043	357.1681	7.334959	63.7975	200	0	0.0018042	0.0187658
1063	357.1831	8.117953	78.9874	200	0	4.97E-04	1.00E-03
2343	358.2412	9.199586	142.785	189	0	1.70E-07	0.020097643
1329	359.1823	6.845587	70.886	200	0	0.00183826	0.03375368
1740	360.1427	7.040306	70.886	199	0	2.77E-04	0.001558058
3904	361.1964	6.682388	57.7215	199	0	0.00111579	0.013765981
649	363.1326	10.65024	189.784	200	0	0.00152486	0.035947785
2529	363.153	9.408391	55.6962	194	0	5.60E-04	0.014934187
3017	363.1797	8.120724	56.7089	198	0	0.04688001	0.027120782
4140	365.1246	4.121747	45.5696	196	0	0.0244768	0.017500656
3737	365.1507	8.112652	51.6456	200	0	0.00245434	0.005698282
2245	365.156	6.791555	59.7468	200	0	0.0168118	0.048100736
3905	365.1954	9.067087	51.6456	200	0	4.90E-07	0.008107309

3092	367.1769	8.174013	63.7975	200	0	0.00381856	0.043078873
3272	368.1882	6.995144	59.7468	200	0	2.60E-04	0.02385819
3008	369.1462	6.983971	54.6835	200	0	0.00570658	0.047773473
2095	370.2117	6.227925	102.278	195	0	7.28E-11	1.40E-04
2313	370.213	6.359656	81.0126	200	0	4.03E-09	0.004400792
693	370.221	5.610689	152.911	200	0	2.15E-06	0.002458166
2024	371.194	8.15404	71.8987	200	0	0.01008115	0.044136927
662	372.2356	7.9477	156.962	200	0	2.94E-04	0.011725034
348	373.1866	8.529893	101.266	200	0	7.53E-05	0.016010977
1020	374.251	7.827888	143.797	195	0	0.01459013	0.012657672
2458	374.2526	8.342021	221.842	200	0	6.22E-05	0.03885404
398	374.255	8.650178	712.622	200	0	8.97E-05	0.00144386
661	376.2692	7.964818	284.924	195	0	2.61E-06	0.005249802
259	377.1472	6.126182	1699.88	200	0	1.22E-14	8.63E-07
1794	377.1499	5.937347	325.255	200	0	9.10E-13	4.14E-06
1778	377.1695	1.418502	73.9241	195	0	8.13E-07	4.67E-05
4015	379.2319	10.24515	45.5696	188	0	2.11E-04	0.001533925
2284	381.1015	2.502113	86.0759	179	0	1.73E-04	5.12E-04
1402	382.1926	6.978212	181.511	200	0	4.81E-04	0.036893867
2577	382.257	11.02732	90.1266	194	0	0.00309362	0.00333819
723	383.1086	5.492982	324.22	197	0	3.05E-08	0.018382946
545	383.1925	4.111277	380.878	199	0	4.50E-04	0.001694456
737	383.2058	3.435644	222.876	199	0	1.01E-06	1.70E-04
2342	385.1976	10.62526	67.8481	197	0	0	3.53E-08
1102	386.9918	2.028266	78.9874	199	0	1.16E-04	0.01790755
1361	387.2152	10.04003	97.2152	198	0	0	4.05E-06
1019	388.1166	4.453347	113.418	199	0	1.41E-11	2.71E-04
1147	389.2438	9.552237	123.544	200	0	0	6.43E-14
1018	390.1997	6.610093	119.494	198	0	3.40E-04	0.00741047
3543	391.1771	6.290856	51.6456	200	0	3.35E-06	6.74E-07
2418	391.1786	6.670113	325.255	200	6.57E-10	2.68E-04	8.08E-04
3681	391.1848	7.047399	55.6962	200	0	1.29E-07	0.004729581
2397	393.16	6.72922	83.038	200	0	1.24E-07	0.001090259
135	393.171	4.749857	889.45	200	0	2.83E-05	1.03E-04
1669	394.8569	0.882504	121.519	200	0	3.30E-11	0.006988282
2268	396.1154	10.31753	64.8101	183	0	8.48E-05	0.030794052
2269	396.1263	7.937308	102.278	191	0	0.01388697	0.04232591
1558	396.1346	7.261147	68.8608	200	0	0.00312339	0.022235252
2646	396.2107	8.133834	74.9367	195	0	0.00156022	0.005170728
690	396.2119	5.618161	227.013	199	0	1.58E-09	0.003676541
3656	397.1567	7.217202	56.7089	198	0	0.0415875	0.049058136
544	397.1576	9.539333	332.493	200	0	2.25E-06	0.038737364
1752	397.1947	5.617948	71.8987	198	0	0.01229748	1.06E-04

504	398.1729	8.195215	147.848	200	0	0.03290619	0.001202573
1774	398.2209	4.116848	75.9493	196	0	0.00991534	0.024519242
2341	399.1319	6.125899	75.9493	198	0	4.44E-16	6.99E-09
1965	399.1858	4.150042	80	199	0	7.49E-05	0.022842074
2234	399.2516	9.185252	71.8987	199	0	0.00543333	0.040732548
4137	400.2615	8.682841	45.5696	192	0	0.00437366	0.003763822
722	400.2685	9.585206	170.136	189	0	0.00255165	0.004773087
3831	400.8104	0.902223	53.6709	198	0	2.97E-11	0.007094598
2873	401.1534	6.464639	59.7468	197	0	0.02131763	0.03415275
503	402.2864	10.141	387.207	197	0	1.69E-06	0.002115462
3040	405.1782	1.636115	99.2405	176	0	1.45E-05	0.012867117
2561	405.1881	6.89819	113.418	199	0	1.16E-07	2.69E-05
2040	406.1659	4.757802	83.038	197	0	4.54E-04	0.045427117
2875	409.0353	8.291355	48.6076	187	0	7.72E-04	0.038076486
3957	409.1213	2.53976	44.557	153	0	3.48E-05	0.002184293
2671	412.1235	2.3475	176.34	163	1.11E-16	3.94E-04	0.005079819
841	412.1264	8.076484	136.709	198	0	1.42E-08	0.023114458
3394	412.1396	4.291708	58.7342	198	0	1.72E-10	0.002642357
625	412.1681	4.515646	182.545	200	0	0.01474212	8.66E-04
3830	412.1765	10.27499	65.8228	185	0	6.25E-05	2.43E-04
1765	412.185	6.152954	63.7975	200	0	3.20E-07	0.04489152
955	413.1308	4.13313	106.329	199	0	7.98E-04	0.039738398
1983	413.1436	9.541053	84.0507	189	0	0.00178681	0.010822217
3511	414.9877	0.996284	82.0253	183	0	2.26E-07	0.003044813
3950	416.2061	6.542873	58.7342	198	0	1.56E-06	0.048632782
4014	417.1669	2.288826	52.6582	178	0	7.38E-06	0.041830756
3829	418.2697	7.862474	56.7089	193	0	0.02531083	0.017484263
2282	419.1814	6.613942	65.8228	199	0	4.98E-04	0.034253605
2093	421.1482	1.291041	88.1013	191	0	2.01E-05	0.001049374
2124	421.1672	5.049445	80	197	0	3.11E-12	4.29E-05
3556	424.169	7.869927	56.7089	194	0	8.03E-04	0.003136611
1454	424.2034	5.3435	112.405	199	0	0.00166324	0.019314196
4136	425.1484	5.604864	48.6076	198	0	0.00575886	0.03969902
2584	425.1835	7.136878	84.0507	200	0	0.00359406	0.007857314
2514	425.2049	3.308369	66.8354	180	0	9.05E-05	3.51E-04
2054	426.2139	5.372275	57.7215	197	0	0.00141334	0.007146644
2746	428.0715	4.457974	55.6962	194	0	4.42E-05	0.04924207
3965	429.2076	8.134089	55.6962	200	0	2.66E-04	0.025198814
3189	430.9613	0.995559	86.0759	184	0	4.42E-08	0.004564597
3720	432.2399	6.980089	54.6835	195	0	6.66E-07	8.59E-05
3471	433.1865	6.564381	50.6329	199	0	0.00110071	0.002071018
1639	435.159	10.10095	176.34	185	0	3.19E-10	0.003561584
2691	435.2176	7.296815	68.8608	199	0	4.18E-08	9.72E-04

602	440.2104	4.340527	290.094	200	0	5.54E-04	0.025441004
1729	440.2213	6.987465	93.1646	199	0	8.83E-04	0.014603507
1683	441.1048	8.763168	86.0759	190	0	8.43E-04	0.044538658
3335	441.1658	5.605665	53.6709	199	0	0.00691033	0.04739631
1097	444.1414	4.617269	332.493	200	0	4.12E-07	0.023619602
1997	444.1737	4.200362	266.309	198	0	2.00E-04	0.008297836
873	444.1762	1.486559	231.149	194	0	4.29E-04	0.033708595
2233	444.2914	9.202499	75.9493	187	0	0.00176628	0.027962934
2176	445.1345	8.618464	235.286	189	0	1.53E-14	1.19E-07
541	447.1013	5.896017	239.422	200	0	1.06E-07	0.007548849
2277	447.2068	7.358049	61.7722	198	0	4.62E-04	6.94E-04
2934	448.1928	6.693928	63.7975	197	0	9.46E-09	0.011094936
2539	454.0957	6.528124	48.6076	200	0	0.00461703	0.003370225
2771	456.8463	0.869835	63.7975	198	0	1.04E-09	0.009555457
3078	458.0837	1.936028	83.038	199	0	7.97E-08	7.43E-04
1098	460.1994	5.934151	217.705	199	0	2.13E-07	0.044190593
256	461.2412	8.915536	198.057	200	0	9.51E-05	6.62E-04
4037	462.8508	0.878798	92.1519	195	0	1.02E-07	0.001385676
3566	465.1507	4.403946	43.5443	195	0	1.91E-10	0.030377084
1210	467.2249	5.389079	71.8987	199	0	0.0023551	0.028881488
2427	468.2406	6.981756	102.278	200	0	4.21E-08	8.58E-06
1477	469.189	4.293579	71.8987	197	0	1.29E-04	0.044839766
3828	473.1754	4.135363	67.8481	189	0	1.25E-05	0.01606024
395	475.2483	8.521787	742.275	200	0	0.02333911	0.01609164
2611	478.2145	5.873382	76.962	196	0	5.40E-08	0.019710895
1636	479.2284	10.40575	61.7722	194	0	4.86E-04	0.005582196
2177	481.1536	6.214264	66.8354	196	0	3.53E-05	4.74E-04
1887	483.2186	1.626655	89.114	185	0	8.23E-05	0.00360836
2906	485.087	6.486163	61.7722	192	0	6.19E-06	0.029670397
720	487.1461	4.083033	155.949	196	0	2.49E-05	0.001138987
812	491.2406	6.954532	152.911	197	0	1.26E-06	0.005492569
914	491.2421	7.507183	228.047	193	0	2.94E-04	1.44E-04
3878	495.0524	8.653729	81.0126	176	0	1.48E-10	0.005994851
2804	499.148	4.839943	57.7215	196	0	6.46E-05	3.23E-06
1276	501.1596	5.380343	97.2152	198	0	0.03088301	3.40E-05
4135	501.2601	6.380909	60.7595	193	0	1.20E-05	3.63E-05
1209	501.2701	9.916751	72.9114	196	0	0.01525901	1.74E-04
1556	503.1243	7.297067	142.785	198	0	0	7.70E-10
232	505.2635	9.071437	260.104	199	0	5.05E-08	1.85E-04
3728	506.2119	6.630759	62.7848	198	0	4.56E-08	0.010846073
3985	507.1193	8.118312	58.7342	188	0	2.89E-11	0.012411991
744	511.2622	4.253147	188.75	197	0	2.00E-04	0.04097449
3011	512.1489	5.657667	54.6835	197	0	0.00179731	0.041031953

2417	512.252	4.257794	66.8354	194	0	1.76E-04	0.001026798
1702	518.2162	5.804041	219.773	196	0	4.40E-10	0.008138615
2855	518.2823	6.959067	68.8608	200	0	1.96E-05	3.38E-04
1338	519.1185	7.99582	180.477	198	0	0	8.14E-08
1178	521.2412	9.071536	113.418	197	0	6.35E-05	3.31E-05
797	523.2543	10.50863	102.278	195	0	1.25E-05	8.04E-05
4091	529.0819	5.353463	68.8608	185	0	1.29E-04	0.028121889
1360	533.1005	4.628623	117.468	199	0	1.00E-06	0.04081653
3266	536.2219	5.801444	58.7342	191	0	4.49E-09	0.003024561
3234	539.1986	5.935065	58.7342	196	0	2.36E-12	5.51E-06
3013	539.2095	6.847483	90.1266	193	0	4.65E-07	2.96E-04
2630	549.0748	4.62871	65.8228	196	0	5.64E-09	0.008661522
231	549.291	9.209442	242.52	198	0	8.22E-07	8.67E-04
1268	550.2408	5.780953	110.38	192	0	0.0299587	0.011038259
2659	551.3566	7.375961	125.57	200	0	0.00279692	0.002148808
1845	553.2582	4.047871	97.2152	190	0	0.007856	0.017692149
3320	554.202	8.104634	58.7342	190	0	2.07E-06	0.020379037
2586	555.1951	6.989527	64.8101	199	0	4.55E-15	2.53E-04
1476	565.2671	9.209575	100.253	199	0	0.00238715	0.005689337
688	567.2799	10.59735	114.43	190	0	1.09E-06	7.30E-04
1475	568.2709	4.252779	143.797	195	0	2.84E-05	0.010905081
3007	571.2135	7.609379	76.962	189	0	3.06E-04	0.044017825
3576	575.2438	5.52496	59.7468	192	0	4.13E-04	0.002845249
4133	584.2652	4.030506	50.6329	191	0	3.29E-04	0.005462584
3387	586.2911	6.847767	73.9241	187	0	5.67E-04	0.004607439
2889	587.2997	10.03991	49.6202	199	0	5.06E-05	0.002709896
1964	589.0565	3.176797	73.9241	168	0	1.25E-05	0.001535266
437	589.3217	10.1388	115.443	196	0	6.10E-04	0.004070472
2829	593.2527	5.938986	103.291	178	0	3.71E-07	0.001638469
287	593.3161	9.333395	174.271	199	0	4.65E-08	3.21E-05
2216	609.2873	9.332852	77.9747	194	0	5.29E-04	5.72E-04
1273	610.3179	5.50187	157.975	195	0	2.46E-04	0.024762422
497	611.3051	10.67593	111.392	194	0	6.00E-05	2.60E-04
536	613.3242	11.73324	112.405	192	0	0.0014714	9.17E-04
2853	625.2899	4.152594	72.9114	195	0	0.00455504	0.024908397
496	633.3461	10.23247	101.266	197	0	0.00868453	0.019196171
3241	636.3635	6.186783	92.1519	187	0	3.34E-14	5.96E-04
872	637.3404	9.445532	102.278	196	0	1.82E-05	2.98E-04
1379	643.3267	7.888749	130.633	200	0	1.76E-04	3.23E-04
1376	655.3292	10.74838	72.9114	194	0	1.69E-04	0.002038542
657	657.3435	11.75283	115.443	197	0	0.00338847	0.014483933
1075	671.3114	3.892134	101.266	200	0	0.00132933	0.012271741
1419	677.3705	10.3162	75.9493	199	0	0.0241807	8.96E-04

3235	681.362	9.547572	57.7215	196	0	9.01E-05	0.018191772
3361	699.3458	10.8143	56.7089	199	0	3.47E-04	7.26E-06
1103	701.3726	11.77729	81.0126	191	0	0.02103337	0.005679218
712	714.1853	1.626574	186.676	193	0	1.10E-04	2.22E-04
1626	779.352	1.414954	348.109	194	0	5.29E-06	0.001765827
1337	786.3605	4.115464	127.595	198	0	0.03612195	0.006587284
2807	795.4505	9.104846	215.618	185	0	9.75E-06	2.54E-06